88-105498

B4

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : C07K 5/02, 5/06, A61K 37/64 — A2

(11) International Publication Number: WO 88/ 02374

(43) International Publication Date: 7 April 1988 (07.04.88)

(21) International Application Number: PCT/US87/02264

(22) International Filing Date: 10 September 1987 (10.09.87)

(31) Priority Application Numbers: 913,490; 925,830; 007,079

(32) Priority Dates: 30 September 1986 (30.09.86); 30 October 1986 (30.10.86); 27 January 1987 (27.01.87)

(33) Priority Country: US

(60) Parent Applications or Grants
(63) Related by Continuation
US 925,830 (CIP) Filed on 30 October 1986 (30.10.86)
US 913,490 (CIP) Filed on 30 September 1986 (30.09.86)
US 007,079 (CIP) Filed on 27 January 1987 (27.01.87)

(71) Applicant (*for all designated States except US*): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*) : SCHOSTAREZ, Heinrich, J. [US/US]; 6417 Surrey, Portage, MI 49002 (US). HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). SAWYER, Tomi, K. [US/US]; 3245 Greenspire, Apt. #10, Portage, MI 49002 (US).

(74) Agent: COX, Martha, A.; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US, US, US.

Published
Without international search report and to be republished upon receipt of that report.

B

(54) Title: RENIN INHIBITORY PEPTIDES HAVING NOVEL C-TERMINAL MOIETIES

(57) Abstract

Novel renin-inhibiting peptides of formula (I): $X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}V$. More particularly the present invention provides renin-inhibiting peptides of the formula (I), wherein A_6, B_7, C_8 and D_9 may represent amino acid residues; E_{10} and F_{11} may represent the 1,4-diamino-1,4-disubstituted-3-hydroxybutane or other stable transition state moieties; X is a terminal group and V is a novel terminal group. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension.

NEW RENIN INHIBITORY PEPTIDES + HAVE [redacted]

NONCLEAVABLE TRANSITION STATE INSERT CORRESP. TO THE 10,11-POSITION OF THE RENIN SUBSTRATE

10-A12C

B(6-D1, 7-H, 10-A8, 10-A9B, 10-A12, 10-A15, 10-A17, 10-A18, 10-A20, 10-B2B, 12-F1B, 12-F1C, 12-F5A, 12-G1B3, 12-K4)

88105498

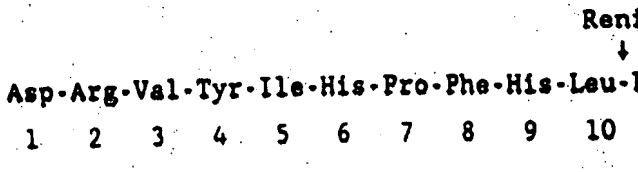
RENIN INHIBITORY PEPTIDES HAVING NOVEL C-TERMINAL MOIETIES

DESCRIPTION

BACKGROUND OF THE INVENTION

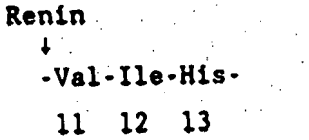
The present invention provides novel compounds. More particularly, the present invention provides renin-inhibiting peptides which have novel moieties at the C-terminus. Most particularly, the present invention provides novel renin-inhibiting peptide analogs which are derived from (1S, 3S, 4S)-1,4-diamino-1,4-disubstituted-3-hydroxy-butane. The present invention also provides renin-inhibitory compounds containing a C-terminal hydroxamate function as compared to the renin substrate. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension.

Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:



IA

as found by L.T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D.A. Tewkesbury et al., Biochem. Biophys. Res. Comm. 99:1311 (1981). It may be represented as follows:



IB

and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin are also useful in the treatment of hypertension.

A number of renin-inhibitory peptides have been disclosed. Thus, U.S. patent 4,424,207, and European published applications 45,665; 104,041; and 156,322; and U.S. patent application, Serial No.

825,250, filed 3 February 1986; disclose certain peptides with the dipeptide at the 10,11-position containing an isostere bond. A number of statine derivatives stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; 114,993; 156,319; and 156,321; and U.S. patents 4,478,826; 4,470,971; 4,479,941; and 4,485,099. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11 position of the renin substrate are disclosed in U.S. patent 4,478,827 and 4,455,303. C-terminal amide cycles are disclosed in U.S. patent 4,485,099 and European published applications 156,320 and 156,318. Certain tetrapeptides are disclosed in European publications 111,266 and 77,029. Further, European published application No. 118,223 discloses certain renin inhibiting peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereodirected "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

Certain dipeptide and tripeptides are disclosed in U.S. patents 4,514,332; 4,510,085; and 4,548,926 as well as in European published applications 128,762; 152,255; and 181,110. Pepstatin derived renin inhibitors have been disclosed in U.S. patent 4,481,192. Retro-inverso bond modifications at positions 10-11 have been disclosed in U.S. patent 4,560,505 and in European published applications 127,234 and 127,235. Derivatives of isosteric bond replacements at positions 10-11 have been disclosed in European published applications 143,746 and 144,290; and U.S. patent application, Serial No. 833,993, filed 27 February 1986. Isosteric bond modifications at positions 11-12 and 12-13 have been disclosed in European published application 179,352. Certain peptides containing 2-substituted statine analogues have been disclosed in European published application 157,409. Certain peptides containing 3-aminodeoxystatine have been disclosed

in European published application 161,588. Certain peptides containing 1-amino-2-hydroxybutane derivatives at positions 10-11 have been disclosed in European published application 172,346. Certain peptides containing 1-amino-2-hydroxypropane derivatives at positions 10-11 have been disclosed in European published application 172,347. Certain peptides containing N-terminal amide cycles have been disclosed in U.S. patent application, Serial No. 844,716, filed 27 March 1986. Certain peptides containing dihalostatine have been disclosed in PCT application, Serial No. 000,713, filed 7 April 1986.

INFORMATION DISCLOSURE

Certain renin inhibitor compounds were disclosed by S.H. Rosenberg, et. al., at an American Chemical Society meeting in New York City on April 13-18, 1986. These peptidic compounds have a transition state moiety of the formula -NH-CH(CH_2R)-CH(OH)CH_2-(CH_2)$_n$-NH-, wherein n is 0 or 1. Published British patent application 2,167,759A discloses certain compounds useful for treating angiotensin related hypotension containing a moiety of the formula NHCHR_2-CHOH-CH_2N-. U.S. patent 4,599,198 discloses renin-inhibitor compounds having a moiety -N-CH(CH_2-cyclohexyl)-CHOH-CH_2-NR_4-. European patent application 181,071 discloses renin inhibitor compounds having a moiety of the formula -NH-CHR_2-CHOH-CH_2-NR_1-.

European published applications 156,322; 114,993; and 118,223; and PCT patent application, Serial No. 002,227, filed 21 October 1986; U.S. patent application, Serial No. 825,250, filed 3 February 1986; PCT patent application, Serial No. 000,291, filed 13 February 1987; and PCT patent application, Serial No. 00,507, filed 13 March 1987; disclose hydroxamic acids or esters at the C-terminus.

SUMMARY OF THE INVENTION

The present invention particularly provides a renin inhibitory peptide of the formula X-A_6-B_7-C_8-D_9-E_{10}-F_{11}-V,

A renin inhibitory peptide having a noncleavable transition state insert corresponding to the 10,11-position of the renin substrate (angiotensinogen) and having a moiety of the formula V, wherein V is

(a) -C(=Y)-G_{12}-H_{13}-Z,

(b) -W,

(c) -G_{12}-H_{13}-W, or

(d) -G_{121}-H_{131}-I_{14}-Z;

corresponding to positions 12 to 14 of the renin substrate;

wherein G_{12} is absent or a divalent moiety of the formula XL_4 or XL_{4a};

wherein G_{121} is absent or a divalent moiety of the formula XL_{41} or XL_{4a1};

wherein H_{13} is absent or a divalent moiety of the formula XL_4;

wherein H_{131} is absent or a divalent moiety of the formula XL_{41};

wherein I_{14} is absent or a divalent moiety of the formula XL_5;

wherein W is

(a) R_{14},

(b) $-C(=Y)-CH_2-Y-R_5$,

(c) $-C(=Y)-YR_5$,

(d) $-C(=Y)(CH_2)_n-R_5$,

(e) $-C(=Y)-(CH_2)_nN-(R_4)_2$,

(f) $-SO_2R_5$,

(g) $-SO_2N(R_4)_2$,

(h) $-C(=Y)(CH_2)_2-SO_2R_5$,

(i) $-C(=Y)-Y-(CH_2)_2-SO_2-R_5$,

(j) $-C(=Y)-NR_4-O-R_5$,

(k) $-C(=NCN)NHR_4$, or

(l) $-C(=Y)(CH_2)_qC(=Y)YR_4$;

wherein each occurrence of Y may be the same or different and Y is

(a) $-O-$,

(b) $-S-$, or

(c) $-NR_4-$;

wherein Z is

(a) $-O-R_{10}$,

(b) $-N(R_4)R_{14}$,

(c) $-C_4-C_8$cyclic amino, or

(d) $-N(R_{10})(OR_{14})$;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,

(c) C_1-C_5alkyl,

(d) C_3-C_7cycloalkyl,

(e) aryl,
(f) -Het,
(g) C_1-C_3alkoxy, or
(h) C_1-C_3alkylthio;

wherein R_4 at each occurrence is the same or different and is
(a) hydrogen, or
(b) C_1-C_5alkyl;

wherein R_5 is
(a) C_1-C_6alkyl,
(b) C_3-C_7cycloalkyl,
(c) aryl,
(d) -Het,
(e) 5-oxo-2-pyrrolidinyl, or
(f) $-C(CH_2OH)_3$;

wherein R_8 is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) hydroxy,
(d) aryl,
(e) -Het,
(f) guanidinyl C_1-C_3alkyl-,
(g) C_3-C_7cycloalkyl, or
(h) $-(CH_2)_p$-C_3-C_7cycloalkyl;

wherein R_9 is
(a) hydrogen,
(b) hydroxy,
(c) amino C_1-C_4alkyl-, or
(d) guanidinyl-C_1-C_3alkyl-;

wherein R_{10} is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_nR_{16}$,
(d) $-(CH_2)_nR_{17}$,
(e) C_3-C_7cycloalkyl,
(f) a pharmaceutically acceptable cation,
(g) $-(CHR_{25})-CH_2-R_{15}$, or
(h) $-CH_2-(CHR_{12})-R_{15}$;

wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is

(a) aryl,

(b) amino,

(c) mono-, di- or tri-C_1-C_3alkylamino,

(d) -Het,

(e) C_1-C_5alkyl,

(f) C_3-C_7cycloalkyl,

(g) C_2-C_5alkenyl,

(h) C_3-C_7cycloalkenyl,

(i) hydroxy,

(j) C_1-C_3alkoxy,

(k) C_1-C_3alkanoyloxy,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) -COOH,

(o) -CO-O-C_1-C_6alkyl,

(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(q) -CO-$NR_{22}R_{26}$,

(r) C_4-C_7cyclic amino,

(s) C_4-C_7cycloalkylamino,

(t) guanidyl,

(u) cyano,

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy C_2-C_4alkyl)amino,

(y) di-(hydroxy C_2-C_4alkyl)amino, or

(z) -CO-$NR_{22}R_{25}$;

wherein R_{14} is

(a) hydrogen,

(b) C_1-C_{10}alkyl,

(c) -$(CH_2)_n$-R_{18},

(d) -$(CH_2)_n$-R_{19},

(e) -(CHR_{25})-CH_2-R_{15},

(f) -CH_2-(CHR_{12})-R_{15},

(g) (hydroxy C_1-C_8alkyl),

(h) (C_1-C_3alkoxy) C_1-C_8alkyl,

(i) -$(CH_2)_n$-aryl,

(j) -$(CH_2)_n$-Het,

(k) $-(CH_2)_{n+2}-R_{18}$, or

(l) $-(CH_2)_{n+2}-R_{19}$;

wherein R_{15} is

(a) hydroxy,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) amino,

(e) mono-, di-, or tri-C_1-C_3alkylamino,

(f) mono- or di-(hydroxy C_2-C_4alkyl)amino,

(g) -Het,

(h) C_1-C_3alkoxy-,

(i) C_1-C_3alkanoyloxy-,

(j) mercapto,

(k) C_1-C_3alkylthio-,

(l) C_1-C_5alkyl,

(m) C_4-C_7cyclic amino,

(n) C_4-C_7cycloalkylamino,

(o) C_2-C_5alkenyloxy, or

(p) C_3-C_7cycloalkenyl;

wherein R_{16} is

(a) aryl,

(b) amino,

(c) mono- or di-C_1-C_3alkylamino,

(d) hydroxy,

(e) C_3-C_7cycloalkyl,

(f) C_4-C_7cyclic amino, or

(g) C_1-C_3alkanoyloxy;

wherein R_{17} is

(a) -Het,

(b) C_2-C_5alkenyl,

(c) C_3-C_7cycloalkenyl,

(d) C_1-C_3alkoxy,

(e) mercapto,

(f) C_1-C_3alkylthio,

(g) -COOH,

(h) $-CO-O-C_1-C_6$alkyl,

(i) $-CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)_2$,

(j) $-CO-NR_{22}R_{26}$,

(k) tri-C_1-C_3alkylamino,
(l) guanidyl,
(m) cyano,
(n) N-cyanoguanidyl,
(o) (hydroxy C_2-C_4alkyl)amino, or
(p) di-(hydroxy C_2-C_4alkyl)amino;

wherein R_{18} is
(a) amino,
(b) mono-, or di-C_1-C_3alkylamino,
(c) C_4-C_7cyclic amino, or
(d) C_4-C_7cycloalkylamino;

wherein R_{19} is
(a) aryl,
(b) -Het,
(c) tri-C_1-C_3alkylamino,
(d) C_3-C_7cycloalkyl,
(e) C_2-C_5alkenyl,
(f) C_3-C_7cycloalkenyl,
(g) hydroxy,
(h) C_1-C_3alkoxy,
(i) C_1-C_3alkanoyloxy,
(j) mercapto,
(k) C_1-C_3alkylthio,
(l) -COOH,
(m) -CO-O-C_1-C_6alkyl,
(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,
(o) -CO-$NR_{22}R_{26}$,
(p) C_4-C_7cycloalkylamino,
(q) guanidyl,
(r) cyano,
(s) N-cyanoguanidyl,
(r) cyanoamino,
(u) (hydroxy C_2-C_4alkyl)amino,
(v) di-(hydroxy C_2-C_4alkyl)amino,
(w) -SO_3H, or
(x) -CO-$NR_{22}R_{25}$;

wherein R_{22} is
(a) hydrogen, or

(b) C_1-C_3alkyl;

wherein R_{25} is

(a) -$(CH_2)_n$-R_{13},

(b) hydrogen,

(c) C_1-C_3alkyl, or

(d) phenyl-C_1-C_3alkyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein for each occurrence n is independently an integer of zero to five inclusive;

wherein p is zero to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di- C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -$N(R_4)$-C_1-C_3alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN,

(t) $-CH_2NH_2$,

(u) $COOR_{25}$, or

(v) $CONHR_{25}$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino, or
(ix) mono- or di- C_1-C_4alkylamino;

or a carboxy-, amino-, or other reactive group-protected form; or a pharmaceutically acceptable acid addition salt thereof.

By "renin inhibitory peptide" is meant a compound capable of inhibiting the renin enzyme in mammalian metabolism and having three or more amino acid residues linked by peptidic or pseudo-peptidic bonds.

By "a non-cleavable transition state insert" is meant a transition state insert which is not cleavable by a hydrolytic enzyme in mammalian metabolism. A variety of such transition state inserts, corresponding to the 10,11-position of the renin substrate, are known in the art, including those disclosed in the following references:

U.S. Patent 4,424,207 (Szelke); European Patent 104041A (Szelke); European Patent Application 144,290A (Ciba Geigy AG); European Patent 0,156,322 (Marck); European Patent 161-588A (Merck); European Patent 0,172,347 (Abbott); European Patent 172-346-A (Abbott); European Patent 156-318 (Merck); European Patent 157-409 (Merck); European Patent 152-255 (Sankyo); and U.S. Patent 4,548,926 (Sankyo); and

U.S. patent application, Serial No. 904,149, filed 5 September 1986; U.S. patent application, Serial No. 844,716, filed 27 March 1986; PCT application, Serial No. 000,713, filed 7 April 1986; U.S. patent application, Serial No. 945,340, filed 22 December 1986; and U.S. patent application, Serial No. 825,250, filed 3 February 1986;

and

A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett et al., J. Am. Chem. Soc., 106:4282 (1984); and Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich. eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

As is apparent to those of ordinary skill in the art, the renin inhibitory peptides of the present invention can occur in several isomeric forms, depending on the configuration around the asymmetric carbon atoms. All such isomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the amino acids corresponds to that of the naturally-occurring amino acids.

These compounds are shown in relation to the human renin substrate as follows:

6	7	8	9	10	11	12	13
-His	Pro	Phe	His	Leu	Val	Ile	His-
X	A_6	B_7	C_8	D_9	E_{10}	F_{11}	V

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmitate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon

atoms, inclusive. Thus (C_1-C_4)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C_4-C_7cyclic amino indicates a monocyclic group containing one nitrogen and 3 to 7 carbon atoms.

Examples of (C_3-C_{10})cycloalkyl which include alkyl-substituted cycloalkyl, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, and cyclohexyl.

Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4- 2,3,6-, or 2,4,5-)trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxyphenyl, and 2,4-dichloro-(5- or 6-)methylphenyl.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, N^{in}-formyl-indolyl, N^{in}-C_2-C_5alkyl-C(O)-indolyl, [1,2,4]-triazolyl, 2-, 4-, 5-pyrimidinyl, 2-, 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

"alo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include:

pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), "Nomenclature and Symbolism for Amino Acids and Peptides," Eur. J. Biochem. 138:9-37 (1984) unless otherwise indicated.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-dependent hypertension, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, renin-dependent hyperaldosterism, angina, post-mycardial infarction and other renin-dependent cardiovascular disorders. The renin-angiotension system may play a role in maintenance of intracellular hemeostasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 0.1 mg to 1000 mg per kg per dose, administered from 1 to 4 times daily. Equivalent dosages for other routes of administration are also employed. For example, renin-associated hypertension and hyperaldosteronism are effectively treated by the administration of from 1.0 to 50 milligrams of the compound per kilogram of body weight per day.

The exact dose depends on the age, weight, and condition of the patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of

pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting compounds may be employed and are described, e.g., in U.S. Patent No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The compounds of the present invention are preferably orally administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or solvated form.

For these purposes the compounds of the present invention may be administered parenterally, by inhalation spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The peptides of this invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive therapy such as diuretics, α and/or β-adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and the like as described for example in published European patent application 156,318.

The present invention is also directed to combinations of the novel renin-inhibitory peptides of Formula I with one or more antihypertensive agents selected from the group consisting of diuretics, α and/or β-adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and other antihypertensive agents.

For example, the compounds of this invention can be given in combination with such compounds or salts or other derivative forms thereof as:

Diuretics: acetazolamide; amiloride; bendroflumethiazide; benzthiazide; bumetanide; chlorothiazide; chlorthalidone; cyclothiazide; ethacrynic acid; furosemide; hydrochlorothiazide; hydroflumethiazide; indacrinone (racemic mixture, or as either the (-) or (-) enantiomer alone, or a manipulated ratio, e.g., 9:1 of said enantiomers respectively); metolazone; methylclothiazide; muzolimine; polythiazide; quinethazone; sodium ethacrynate; sodium nitroprusside; spironolacetone; ticrynaten; trimaterene; trichlormethiazide;

α-Adrenergic Blocking Agents: dibenamine; phentolamine; phenoxybenzamine; prazcsin; tolazoline;

β-Adrenergic Blocking Agents: atenolol; metoprolol; nadolol; propranolol; timolol;

((±)-2-[3-(tert-butylamino)-2-hydroxypropoxy]-2-furananilide)(oncarolol);

(2-acetyl-7-(2-hydroxy-3-isopropyaminopropoxy)benzofuran HCl)(befunolol);

((±)-1-(isopropylamino)-3-(p-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propranol HCl) (betaxolol);
(1-[(3,4--dimethoxyphenethyl)amino[-3-(m-tolyloxy)-2-propanol HCl) (bevantolol);
(((±)-1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-isopropylamino-2-propanol)fumarate) (bisoprolol);
(4-(2-hydroxy-3-[4-(Phenoxymethyl)-piperidino]-propoxy)-indole;
(carbazolyl-4-oxy-5,2-(2-methoxyphenoxy)-ethylamino-2-propanol);
(1-((1,1-dimethylethyl)amino)-3-((2-methyl 'H-indol-4-yl)oxy)-2-propanol benzoate) (bopindolol);
(1-(2-exobicyclo[2.2.1]-hept-2-ylphenoxy)-3-[(1-methylethyl)-amino]-2-propanol HCl) (bornaprolol);
(o-[2-hydroxy-3-[(2-indol-3-yl-1,1-dimethylethyl)-amino]propoxy]benzonitrile HCl) (bucindolol);
(α-[(tert butylamino)methyl]-7-ethyl-2-benzofuranmethanol) (bufuralol);
(3-[3-acetyl-4-[3-(tert.butylamino)-2-hydroxypropyl]-phenyl]-1,1-diethylurea HCl) (celiprolol);
((±)-2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-methylacetamide HCl) (cetamolol);
(2-benzimidazolyl-phenyl(2-isopropylaminopropanol));
((±-3'-acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide HCl) (diacetolol);
(methyl-4-[2-hydroxy-3-[(1-methylethyl)aminopropoxyl]]-benzenepropanoate HCl) (esmolol);
(erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol);
(1-(tert.butylamino)-3-[O(2-propynyloxy)phenoxy]-2-propanol (pargolol);
(1-(tert.butylamino)-3-[o-(6-hydrazino-3-pyridazinyl)phenoxy]-2-propanol diHCl) (prizidilol);
((-)-2-hydroxy-5-[(R)-1-hydroxy-2-[(R)-(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide);
(4-hydroxy-9-[2-hydroxy-3-(isopropylamino)-propoxy]-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one) (iprocrolol);
((-)-5-(tert.butylamino)-2-hydroxypropoxy]-3,4-dihydro-1-(2H)-naphthalenone HCl) (levobunolol);
(4-(2-hydroxy-3-isopropylamino-propoxy)-1,2-benzisothiazole HCl);
(4-[3-(tert.butylamino)-2-hydroxypropoxy]-N-methylisocarboxtyril

HCl);
((±)-N-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]ethyl-N'-isopropylurea) (pafenolol);
(3-[[(2-trifluoroacetamido)ethyl]amino]-1-phenoxypropan-2-ol);
(N-(3-(o-chlorophenoxy)-2-hydroxypropyl)-N'-(4'-chloro-2,3-dihydro-3-oxo-5-pyridazinyl)ethylenediamine);
((±)-N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyphenyl]-butanamide) (acebutolol);
((±)-4'-[3-(tert-butylamino)-2-hydroxypropoxy]spiro[cyclohexane-1,2'-indan]-1'-one) (spirendolol);
(7-[3[[2-hydroxy-3-[(2-methylindol-4-yl)oxylpropyl]amino]butyl]thiophylline) (teoprolol);
((±)-1-tert.butylamino-3-(thiochroman-8-yloxy)-2-propanol);
((±)-1-tert.butylamino-3-(2,3-xylyloxy)-2-propanol HCl) (xibenolol);
(8-[3-(tert.butylamino)-2-hydroxypropoxy]-5-methylcourmarin) (bucumolol);
(2-(3-(tert.butylamino)-2-hydroxy-propoxy)benzonitrile HCl) (bunitrolol);
((±)-2'-[3-(tert-butylamino)-2-hydroxypropoxy-5'-fluorobutyrophenone) (butofilolol);
(1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol) (carazolol);
(5-(3-tert.butylamino-2-hydroxy)propoxy-3,4-dihydrocarbotyril HCl) (carteolol);
(1-(tert.butylamino)-3-(2,5-dichlorophenoxy)-2-propanol) (clorano-lol);
(1-(inden-4(or 7)-yloxy)-3-(isopropylamino)-2-propanol HCl) (indenolol);
(1-isopropylamino-3-[(2-methylindol-4-yl)oxy]-2-propanol) (mepindolol);
(1-(4-acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol) (metipranolol);
(1-(isopropylamino)-3-(o-methoxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol) (moprolol);
((1-tert.butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) (nadolol);
'(S)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol sulfate (2:1)) (penbutolol);
(4'-[1-hydroxy-2-(amino)ethyl]methanesulfonanilide) (sotalol);

(2-methyl-3-[4-(2-hydroxy-3-tert.butylaminopropoxy)phenyl]-7-methoxy-isoquinolin-1-(2H)-one);
(1-(4-(2-(4-fluorophenyloxy)ethoxy)phenoxy)-3-isopropylamino-2-propanol HCl);
((-)-p-[3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-β-methyl-cinnamonitrile) (pacrinolol);
((±)-2-(3'-tert.butylamino-2'-hydroxypropylthio)--(5'-carbamoyl-2'-thienyl)thiazole HCl) (arotinolol);
((±)-1-[p-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-isopropylamino)-2-propanol) (ciclopolol);
((±)-1-[(3-chloro-2-methylindol-4-yl)oxy]-3-[(2-phenoxyethyl)amino]-2-propanol) (indopanolol);
((±)-6-[[2-[[3-(p-butoxyphenoxy)-2-hydroxypropyl]amino]ethyl]amino 1,3-dimethyluracil) Ipirepolol);
(4-(cyclohexylamino)-1-(1-naphtholenyloxy)-2-butanol);
(1-phenyl-3-[2-[3-(2-cyanophenoxy)-2-hydroxypropyl]aminoethyl]hydratoin HCl);
(3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran) (nipradolol);

Angiotensin I Converting Enzyme Inhibitors:
1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (captopril);
(1-(4-ethoxycarbonyl-2,4(R,R)-dimethylbutanyl)indoline-2(S)-carboxylic acid);
(2-[2-[(1-(ethoxycarbonyl)-3-phenyl-propyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid);
((S)-1-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid HCl);
(N-cyclopentyl-N-(3-(2,2-dimethyl-1-oxopropyl)thiol-2-methyl-1-oxopropyl)glycine) (pivalopril);
((2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidine-carboxylic acid);
(1-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(s)-alanyl)-cis,syn-octahydroindol-2(S)-carboxylic acid HCl);
((-)-(S)-1-[(S)-3-mercapto-2-methyl-1-oxopropyl[indoline-2-carboxylic acid);
([1(S), 4S]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-phenylthio-L-proline;
(3-((1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-

2-oxo-1-(3S)-benzazepine-1-acetic acid HCl);
(N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine) and the S-methyl analogue;
(N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate) (enalapril);
N-1-(S)-carboxy-3-phenylpropyl]-L-alanyl-1-proline;.
N^2-[1-(S)-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lysinopril);
Other Antihypertensive Agents: aminophylline; cryptenamine acetates and tannates; deserpidine; meremethoxylline procaine; pargyline; trimethaphan camsylate; and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. Coadministration is most readily accomplished by combining the active ingredients into a suitable unit dosage form containing the proper dosages of each. Other methods of coadministration are, of course, possible.

The novel peptides of the present invention possess an excellent degree of activity in treating renin-associated hypertension and hyperaldosteronism.

The compounds of the present invention may be pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

The compounds of the present invention are preferably administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated form.

In appropriate cases, micronization of the compounds of this invention may be advantageous for optimal drug delivery.

The compounds of the present invention are prepared as depicted in the charts and as described more fully in the Preparations and Examples.

CHART A

The starting materials for the compounds of this invention are

prepared by the Curtius rearrangement of the (2S, 4S, 5S)-5-(t-butoxycarbonylamino)-4-(t-butyldimethylsilyloxy)-2,5-disubstituted-pentanoic acids according to Chart A. (See published European patent application 173,181A, published 5 March 1986). In Chart A, V_1 is the appropriate residue necessary to prepare a final compound having a substituent within the definition of V, and all other variables are as defined above. In this process, the compounds of formula A-1 are treated with isobutyl chloroformate and triethylamine to give the mixed anhydrides (A-2) which without isolation are allowed to react with sodium azide. The resulting acyl azides (A-3) are isolated from the aqueous reaction mixture, dried and warmed with benzyl alcohol to give the carbamates A-4 via the isocyanates A-5. Both A-4 and A-5 are useful intermediates for compounds of formula I. Deprotection of the carbamates A-4 by hydrogenolysis of the benzyl moiety gives the amines A-6 which will react with activated carboxylic acids to give amides A-7, with isocyanates to give ureas A-8, with isothiocyanates to give thioureas A-9 and with chloroformates to give carbamates A-10. Guanidines A-11 are prepared by the successive reactions of the thioureas A-9 with an alkylating agent and an appropriate amine. Alternatively, the isocyanate intermediates A-5 will react with amines or alcohols to give the corresponding ureas or carbamates. The resulting intermediates can be used to prepare the compounds of formula I by the usual methods for peptide synthesis.

The process of the present invention is also more completely understood by reference to the Charts B and C. In these charts, the variables are as defined above, and in Chart C, R is defined as methyl, ethyl, phenyl or benzyl.

CHART B

Chart B describes the preparation of the fully protected peptidic acid, Bob-Phe-His(Tos)-OH, which is useful as an intermediate in the synthesis of renin inhibitors. The compound of formula B-1 is treated with p-nitrophenol and dicyclohexylcarbodiimide in ethyl acetate at 0°C for about one hour. Other activating reagents such as N-hydroxysuccimide or 1,1-carbonyldiimidizole may be utilized with condensing reagents known in the art such as diisopropylcarbodiimide, diethylphosphoryl cyanide or N-methyl-2-halopyridinium salts. Suitable solvents include tetrahydrofuran, glyme, and halocarbons such as dichloromethane and chloroform. The

compound of formula B-2 is isolated by standard procedures known in the art.

The compound of formula B-2 is reacted with His-methyl ester hydrochloride and base in dimethylformamide at room temperature for about eighteen hours. Suitable bases include hindered tertiary amines such as triethylamine or diisopropylethylamine. The compound of formula B-3 is isolated by standard procedures known in the art. The compound of formula B-3 is treated with tosyl chloride and base in methylene chloride at room temperature for about one hour. Bases suitable in this transformation are similar to those described above, tertiary amines. Suitable solvents include tetrahydrofuran, ethyl acetate, diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. The compound of formula B-4 is isolated by standard procedures known in the art.

The compound of formula B-4 is treated with lithium hydroxide in tetrahydrofuran/water at room temperature for about thirty minutes. The compound of formula B-5 is isolated by standard procedures known in the art.

CHART C

Chart C illustrates the preparation of renin-inhibitory peptides containing a C-terminal hydroxamate function. The compounds of formula C-1 and C-1A are treated with a condensing reagent and base in methylene chloride at 0°C to room temperature for 30 min. to 24 hrs. Suitable solvents include tetrahydrofuran, ethyl acetate, diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. Suitable bases include hindered tertiary amines such as triethylamine or diisopropylethylamine. The compound of formula C-2 is isolated by standard procedures known in the art.

The compound of formula C-2 is deprotected using acidic conditions. Those most commonly employed include 2:1 to 1:1 mixtures of methylene chloride:trifluoroacetic acid or dry hydrochloric acid in 1,4-dioxane or diethyl ether.

Condensation with the next reactant is carried out as described above. Namely, the compounds are treated with a condensing reagent and base in methylene chloride at 0°C to room temperature for 30 min. to 24 hrs. Suitable solvents include tetrahydrofuran, ethyl acetate, diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. Suitable bases include hindered tertiary amines such as

triethylamine or diisopropylethylamine. The compound of formula C-3 is isolated by standard procedures known in the art.

This procedure may be repeated to deliver the compounds of formula C-4. The compound of formula C-4 is isolated by standard procedures known in the art.

Removal of the p-toluenesulfonyl protecting group on histidine may be accomplished by nucleophilic displacement. This may be carried out with nucleophiles such as 1-hydroxybenzotriazole in protic solvents such as methanol, or with reagents such as tetra-N-butylammonium fluoride in aprotic solvents such as tetrahydrofuran. Times range from 30 min. to 48 hrs. at temperatures ranging from 20° to 50°C. The compound of formula C-5 is isolated by standard procedures known in the art.

Generally, the renin inhibiting polypeptides may be prepared by either polymer assisted or solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. Appropriate protecting groups, reagents, and solvents for both the solution and solid phase methods can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983; "Solid Phase Peptide Synthesis", J.M. Stewart and J.D. Young, Pierce Chemical Company, Rockford, Ill., 1984; "The Practice of Peptide Synthesis", M. Bodansky and A. Bodansky, Springer-Verlag, New York, 1984; "The Principles of Peptide Synthesis", M. Bodansky, Springer-Verlag, New York, 1984. For example, the carboxylic moiety of N^{α}-t-butyloxycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid, peptide or polymer-bound peptide using a conventional coupling protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are also described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 4,485,099, which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completing, the N^{α}-Boc moiety may be selectively removed with 50% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride. In the case of polymer-assisted peptide synthesis, this stepwise, coupling strategy may be partially or completely automated to provide the desired peptide-polymer intermediates. Anhydrous hydrofluoric acid treatment of the peptide-polymer intermediates may then be used to effect simultaneous protecting group removal and cleavage of the peptide from its polymeric support. A notable exception to this includes N^{in}-formyl-indolyl-substituted peptides in which the N^{in}-formyl-indolyl moiety is stable to TFA or hydrogen fluoride but may be removed by ammonia or sodium hydroxide. Because N^{in}-formyl-tryptophane (FTrp) is somewhat unstable to base in synthetic procedures, possibly causing lower yields, it may be desirable in solution phase synthesis to introduce the FTrp-containing moiety late in the synthetic sequence so that it is not exposed to such conditions.

The incorporation of N^{in}-formyl-Trp into compounds of the present invention is easily accomplished because of the commercial availability of N^{α}-Boc-N^{in}-formyl-Trp-OH. However, the N^{in}-formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with hydrochloric-formic acid as reported in the literature, see A. Previero et al, Biochim. Biophys. Acta 147, 453 (1967); Y.C.S. Yang et al, Int. J. Peptide Protein Res. 15, 130 (1980).

Generally, methods of alkylation useful in alkylating histidine for use in the present invention are found in Cheung, S.T. et al., Can. J. Chem., Vol 55, pp. 906-910 (1977). However it is now found that in the Cheung, S.T. et al, method, it is critical that the reaction conditions for the alkylation of histidine be anhydrous. Further, it is now found also that during work-up instead of adding water directly to the reaction mixture, it is preferred that a buffered aqueous solution be added to the reaction mixture, for example, aqueous sodium or potassium hydrogen sulfate.

Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily

skilled chemist or are readily available in the literature.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

Certain compounds of this invention are preferred. Compounds of the Formula I, wherein V is W and W is $-C(=Y)-YR_5$ or $-C(=Y)-NR_4-O-R_5$, and Y is -O- or -S- are preferred. Thus (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(isopropylamino)carbonyl]-amino]nonane; and

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(methoxyamino)carbonyl]-amino]nonane are preferred.

Also preferred are compounds of the formula I, wherein V is $-G_{121}-H_{131}-I_{14}-Z$ and Z is $-N(R_{10})(OR_{14})$. Thus

Boc-Phe-His-Sta-Ile-$NHOCH_3$, or L-Histidinamide, N-[(1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[-[(methoxyamino)carbonyl]-2-methylbutyl]amino]-1-(2-methylpropyl)-(4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-;

Boc-Phe-His-Sta-Ile-$NHOC_2H_5$, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-[[1-[(ethoxyamino)carbonyl]-2-methylbutyl]amino]-2-hydroxy-1-(2-methylpropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-;

Boc-Phe-His-LVA-Ile-$NHOCH_2$-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(phenylmethoxy)amino]carbonyl]butyl]amino]carbonyl]-1-(2-methylpropyl)hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-; are preferred.

In the Preparations and Examples below and throughout this document:

^{1}H-NMR is nuclear magnetic resonance

Amp is 2-(aminomethyl)pyridinyl

Bn is benzylester

BOC is t-butoxycarbonyl

Bz is benzyl

C is centigrade

Cbz is benzyloxycarbonyl

$CDCl_3$ is deuteriochloroform

Celite is a filter aid

DCC is dicyclohexylcarbodiimide

DEPC is diethylphosphoryl cyanide

EtOAc is ethyl acetate

FTrp is N^{in}-formyl-Trp

g is grams

His is histidine

HOBT is 1-hydroxybenzotriazole

HPLC is high performance liquid chromatography

Ile is isoleucine

IR is infrared spectra

LVA is Leuψ(CH(OH)CH_2)Val with the S configuration at C4 (the hydroxyl-bearing carbon atom)

M or mol is mole

Me is methyl

min. is minute

ml is milliliter

MPLC is medium pressure liquid chromatography

MS is mass spectroscopy

Ph is phenyl

Phe is phenylalanine

RIP means a compound having the formula H-Pro-His-Phe-His-Phe-Phe-Val-Tyr-Lys-OH.$_2(CH_3C(O)OH)$.-XH_2O which is a known renin-inhibiting peptide.

Sta is statine

TBS or TBDI7S is tert-butyldimethylsilyl

TEA is triethylamine

TFA is trifluoroacetic acid

THF is tetrahydrofuran

TLC is thin layer chromatography

Tos is p-toluenesulfonyl

TsOH is p-toluenesulfonic acid.

The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is seen fully by the Examples below.

The following general procedures are employed for preparing the compounds of this invention.

Procedure A - Coupling of an acid to an amine with 1-hydroxybenzotriazole and dicylohexylcarbodiimide

To a nitrogen (N_2) covered solution of the amine free base in methylene chloride is added in turn the acid, 1-hydroxybenzotriazole (HOBT) and dicyclohexylcarbodiimide (DCC). The mixture is stirred at room temperature and then filtered. The filtrate is concentrated in vacuo and the residue is treated with ethyl acetate and filtered again. The filtrate is washed once with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated in vacuo. The residue is then chromatographed on silica gel to yield the coupled product.

Procedure B - Coupling of an acid to an amine using Mukaiyama conditions.

To a nitrogen covered solution of the amine free base in methylene chloride is added 1.5 equivalents of the acid followed by 2.4 equivalents of diisopropylethylamine (Hunig's Base) and 1.2 equivalents of 2-chloro-1-methylpyridinium iodide (Mukaiyama Salt). The mixture is heated at reflux for 1 hr, allowed to cool and diluted to twice its volume with methylene chloride. The solution is washed with aqueous sodium bicarbonate and dilute brine, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed over silica gel to yield the coupled product.

Procedure C - Boc group removal

A 5% solution of the Boc protected amine in an equal volume of methylene chloride and trifluoroacetic acid is allowed to stand at room temperature and then concentrated in vacuo. The residue is

dissolved in methylene chloride or ethyl acetate and washed once with aqueous sodium bicarbonate and dilute aqueous sodium chloride, dried over magnesium sulfate and concentrated in vacuo. The residue is either chromatographed over silica gel or used as is in the next step.

Procedure D - Coupling an acid to an amine using diethyl cyanophosphonate.

To a nitrogen covered 0.04 molar solution of the free amine in methylene chloride is added 1.25 equivalents of the acid followed by 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate. The solution is allowed to stir at room temperature for 2-3 hours, diluted with methylene chloride and washed once with aqueous $NaHCO_3$. The aqueous fraction is backwashed twice with methylene chloride. The organic fractions are combined, dried over magnesium sulfate and concentrated in vacuo. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure E - Coupling an acid to an amine using diethyl cyanophosphonate

To a nitrogen covered 0.04 molar solution of the acid in methylene chloride is added 1.25 equivalents of the amine followed by 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate. The solution is allowed to stir at room temperature for 2-3 hours, diluted with methylene chloride and washed once with aqueous sodium bicarbonate. The aqueous fraction is backwashed twice with methylene chloride. The organic fractions were combined, dried over magnesium sulfate and concentrated in vacuo. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure F - Boc Group Removal

A 5% solution of the Boc protected amine in an equal volume of methylene chloride and trifluoroacetic acid is allowed to stir at room temperature for 1 hour and then concentrated in vacuo. A solution of the residue in methylene chloride is washed once with aqueous sodium bicarbonate. The aqueous wash is backwashed twice with methylene chloride. The combined organic fractions are dried over magnesium sulfate and concentrated in vacuo. The residue is then used as is in the next step without further purification.

Preparation 1 (3S,5S,6S)-3-(Benzyloxycarbonylamino)-6-(t-butoxycarbonylamino)-5-(t-butylidimethyl-silyl-

oxy)-2,8-dimethylnonane.

To a N_2 covered ice bath cooled solution of 0.5 g (1.12 mmol) of the acid (Compound A-1, Chart A) in 7.0 ml of acetone, 0.55 ml of H_2O and 0.172 ml (1.23 mmol) of triethylamine is added 0.160 ml (1.23 mmol) of isobutylchloroformate. After stirring in the cold for 30 min there is added a solution of 0.365 g of sodium azide in 2.0 ml of H_2O over 3 min. After stirring for an additional hour in the cold, the mixture is pipetted into 15 ml of ice water. The resulting mixture is extracted 3 times with ice cold EtOAc. The combined extracts are dried over $MgSO_4$ and concentrated in vacuo. The residue is concentrated 2 additional times from benzene and allowed to stand for 18 hrs in vacuo. A solution of the residue in 5 ml of benzyl alcohol is heated to 90-95° in an oil bath for 2 hrs 50 min, allowed to cool and then concentrated in vacuo. The residue is chromatographed over silica gel using 7.5% EtOAc:hexane to yield 0.416 g (67.4%) of rearranged product. The NMR compares with material from another run, the structure of which is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 551. Theory for $C_{30}H_{55}N_2O_5Si$, 551.3880; Measured, 551.3903.

Example 1 (3S,5S,6S)-3-(Benzyloxycarbonylamino)-6-[[N^{α}-[N^{α}-(t-butoxycarbonyl)phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane.

Part A.

By the general procedure C for Boc group removal, 0.209 g (0.379 mmol) of the Boc amino urethane (Preparation 1) yields 0.204 g of the crude free amine. The amine is then coupled (procedure B) with Boc(tosyl)histidine. The chromatography is carried out using 1.8% MEOH:CH_2Cl_2 containing 0.18% of NH_4OH to yield 0.254 g (79.6%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 842; Theory for $C_{43}H_{68}N_5O_8SSi$, 842.4558; Measured, 842.4544.

Part B.

By the general procedure C for Boc group removal, 0.254 g (0.302 mmol) of Boc peptide from Part A yields 0.201 g of crude free amine. The amine is then coupled (procedure B) with Boc phenylalanine and chromatographed with 3% MEOH:CH_2Cl_2 containing 0.3% NH_4OH to yield

0.241 g of coupled product contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 875; Theory for $C_{46}H_{63}N_6O_9S$, 875.4377; Measured, 875.4354.

Part C.

To a N_2 covered solution of 0.233 g of the tosyl protected peptide mixture from the previous reaction (Part B) in 2.6 ml of DMF and 13 ml of THF is added 0.36 (2.66 mmol) of 1-hydroxybenzotriazole. After stirring at room temperature for 25 hrs the mixture is concentrated in vacuo. The residue is chromatographed over silica gel using 5% MEOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.147 of the above named peptide. The structure is supported by high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 721; Theory for $C_{39}H_{57}N_6O_7$, 721.4288; Measured, 721.4273.

Example 2 (3S,5S,6S)-3-Amino-6-[[N^{α}[N^{α}-(t-butoxycarbonyl-)L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane.

A mixture of 0.096 g (0.133 mmol) of the CBZ peptide (Example 1) and 0.05 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 2 hrs 15 min. An additional 0.05 g of 10% Pd/C catalyst is added and stirring is continued for an additional 18 hrs. The catalyst is removed by filtration and the filtrate concentrated in vacuo. The residue is chromatographed over silica gel using 30% MEOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.062 g (79.4%) of the title compound. The structure is supported by high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 587; Theory for $C_{31}H_{51}N_6O_5$, 587.3921; Measured, 587.3896.

Example 3 (3S,5S,6S)-6-[[N^{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isopropoxycarbonyl)amino]nonane.

Part A.

A mixture of 0.203 g (0.369 mmol) of CBZ peptide (Preparation 1) and 0.10 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 2 hrs 45 min. The catalyst is removed by filtration and the filtrate is concentrated in vacuo to yield 0.146 g (94.9%) of free amine. The structure is supported by NMR and high

resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 417; Theory for $C_{22}H_{49}N_2O_3Si$, 417.3512; Measured, 417.3531.

Part B.

To a N_2 covered, ice bath cooled solution of 0.092 g (0.221 mmol) of the free amine (Part A) and 0.077 ml of triethylamine in 4 ml of THF is added 0.055 ml of isopropylchloroformate. The ice bath is allowed to melt and the mixture is then stirred at room temperature for 16 hrs. The reaction mixture is then pipetted into 10 ml of ice water and then extracted three times with CH_2Cl_2. The combined extracts are dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed over silica gel using 10% EtOAc:haxane to yield 0.091 g (81.9%) of the urethane. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 503; Theory for $C_{26}H_{55}N_2O_5Si$, 503.3880; Measured, 503.3907.

Part C.

By the general procedure C for Boc group removal, 0.086 g (0.171 mmol) of the Boc peptide (Part B) yields 0.091 of the crude amine. The amine is then coupled with Boc(Tosyl)-histidine (procedure B) and chromatographed using 2% MEOH:CH_2Cl_2 containing 0.2% NH_4OH to yield 0.116 g (85.4%) of the coupled peptide. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 794; Theory for $C_{39}H_{68}N_5O_8SSi$, 794.4558; Measured, 794.4565.

Part D.

According to the general procedure C for Boc group removal. 0.113 g (0.142 mmol) of the Boc amine (Part C) yields 0.087 g of crude free amine. This amine is then coupled (procedure B) with Boc phenylalanine and chromatographed using 3% MEOH:CH_2Cl_2 containing 0.3% NH_4OH to yield 0.115 g of coupled peptide contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 827; Theory for $C_{42}H_{63}N_6O_4S$, 827.4377; Measured, 827.4383.

Part E.

To a N_2 covered solution of 0.113 g of the tosyl protected peptide mixture from the previous reaction (Part D) in 1.3 ml of DMF

and 7.0 ml of THF is added 0.18 g (1.37 mmol) of 1-hydroxybenzotriazole. After stirring at room temperature for 22 hrs the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 5% MEOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.061 g of titled product. The structure is supported by NMR and high resolution mass spec.

Found: $[m \cdot + H]^+$ at m/z 673; Theory for $C_{35}H_{57}N_6O_7$, 673.4288; Measured, 673.4293.

Example 4 (3S,5S,6S)-6-[[N^{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(3-methyl-1-oxobutyl)amino]nonane.

Part A.

By coupling procedure A, 0.20 g (0.48 mmol) of the amine (Example 3, part A) is coupled with isovaleric acid using 1.5 equivalents of the acid, HOBT and DCC. After a reaction time of 2.25 hrs, an additional 1.5 equivalents of the acid, HOBT and DCC are added and the reaction is continued for 17 hrs. At this time, 5 ml of DMF is added and stirring is continued for an additional 1 hr 40 min. The reaction is then worked up according to the standard procedure and chromatographed over silica gel using 10% EtOAc:hexane to yield 0.248 g (103%) of coupled product containing some unknown extraneous material. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 501; Theory for $C_{27}H_{57}N_2O_4Si$, 501.4087; Measured, 501.4051.

Part B.

Using the general procedure C for Boc group removal, 0.248 g of the material from the previous reaction (Part A) yields 0.160 g of crude free amine. The amine is then coupled (procedure B) with Boc-(tosyl)histidine and chromatographed using 1.8% MEOH:CH_2Cl_2 containing 0.18% NH_4OH to yield 0.252 g of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 792; Theory for $C_{40}H_{70}N_5O_7SSi$, 792.4765; Measured, 792,4739.

Part C.

By the general procedure C for Boc group removal, 0.252 g (0.318 mmol) of the Boc peptide (Part B) yields 0.203 g of the crude free amine. The amine is then coupled (procedure B) with Boc phenyl-

alanine and chromatographed using 3% MeOH:CH_2Cl_2 containing 0.3% NH_4OH to yield 0.187 g (71.3%) of the coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 825; Theory for $C_{43}H_{65}N_6O_8S$, 825.4584; Measured, 825.4590.

Part D.

To a N_2 covered solution of 0.187 (0.227 mmol) of the tosyl protected peptide (Part C) in 2.2 ml of DMF and 11.5 ml of THF is added 0.31 g (2.27 mmol) of 1-hydroxybenzotriazole. After stirring at room temperature for 22 hrs the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 6.25% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to give 0.119 g (78.1%) of the titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 671; Theory for $C_{36}H_{59}N_6O_6$, 671.4496; Measured, 671.4501.

Example 5 (3S,5S,6S)-3-[[N^{α}[N^{α}-(Benzyloxycarbonyl)-D-valyl)]-amino]-6-[[N^{α}-[N^{α}-(t-butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane.

Part A.

Using coupling procedure B, 0.10 g (0.24 mmol) of the amine (Example 3, Part A) is coupled with CBZ-D-valine and chromatographed with 15% EtOAc:hexane to yield 0.131 g (84.0%) of the coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 650; Theory for $C_{35}H_{65}N_3O_6Si$, 650.45646; Measured, 650.4540.

Part B.

According to the general procedure C for Boc group removal, 0.291 g (0.448 mmol) of the Boc peptide (Part A) yields 0.287 g of the crude free amine. The amine is then coupled (procedure B) to Boc(tosyl)histidine and chromatographed using 1.8% MeOH:CH_2Cl_2 containing 0.18% NH_4OH to yield 0,349 g (81.1%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 941; Theory for $C_{48}H_{77}N_6O_9SSi$, 941.52426; Measured, 941.5212.

Part C.

By the general procedure C for BOC group removal, 0.342 g (0.363

mmol) of the Boc peptide (Part B) yields 0.306 g of the crude free amine. The amine is then coupled (procedure B) to Box phenylalanine and chromatographed using 3.5% MeOH:CH_2Cl_2 containing 0.35% NH_4OH to yield 0.343 g of crystalline material (m.p. 183-191°) contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 974. Theory for $C_{51}H_{72}N_7O_{10}$, 974,5061; Measured, 974.5030.

Part D.

To a N_2 covered solution of 0.341 g of the tosyl protected mixture from the previous reaction (Part C) in 3.4 ml of DMF and 17 ml of THF is added 0.47 g (3.5 mmol) of 1-hydroxybenzotriazole. After stirring for 16 hr the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 5% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.253 g of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 820. Theory for $C_{44}H_{66}N_7O_8$, 820.4973; Measured, 820.4950.

Example 6 (3S,5S,6S)-6-[[N$^{\alpha}$[N$^{\alpha}$-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(D-valyl)amino]nonane.

A mixture of 0.137 g (0.167 mmol) of the CBZ amine (Example 5) and 0.06 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 35 min. An additional 0.06 g of catalyst is added and stirring is continued for 19 hr. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is chromatographed over silica gel with 6% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.094 (82.1%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 686. Theory for $C_{36}N_{60}N_7O_6$, 686.4605; Measured, 686,4601.

Example 7 (3S,5S,6S)-3-[[N$^{\alpha}$-[(3-Aminomethyl)benzoyl]-D-valyl]-amino]-6-[[N$^{\alpha}$[N$^{\alpha}$-(t-butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane.

Part A.

A mixture of 0.131 g (0.202 mmol) of CBZ amine (Example 5, Part A) and 0.05 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 1.2 hr. The catalyst is removed by

filtration and the filtrate concentrated in vacuo to yield 0.101 g (96.9%) of free amine. The structure is supported by NMR.

Part B.

By coupling procedure B, 0.101 g (0.196 mmol) of the free amine (Part A) is coupled with 3-cyanobenzoic acid and chromatographed with 1.25% MeOH:CH_2Cl_2 containing 0.125% NH_4OH to yield 0.112 g (88.6%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 645. Theory for $C_{35}H_{61}N_4O_5Si$, 645.4411; Measured, 645.4382.

Part C.

By the general procedure C for Boc group removal, 0.112 g (0.174 mmol) of the Boc peptide (Part B) yields 0.090 g of the free amine. The amine is then coupled (coupling procedure B) with Boc(tosyl)histidine and chromatographed with 1.75% MeOH:CH_2Cl_2 containing 0.175% NH_4OH to yield 0.134 g (82.3%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 936. Theory for $C_{48}H_{74}N_7O_8SSi$, 936.5089; Measured, 936.5063.

Part D.

By the general procedure C for Boc group removal, 0.129 g (0.138 mmol) of the Boc peptide (Part C) yields 0.110 g of the free amine. The amine is then coupled (coupling procedure B) with Boc phenylalanine and chromatographed with 3.5% MeOH:CH_2Cl_2 containing 0.35% NH_4OH to yield 0.124 g of coupled product mixed with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 969. Theory for $C_{51}H_{69}N_8O_9S$, 969.4908; Measured, 969.4945.

Part E.

To a N_2 covered solution of 0.124 g of the peptide mixture from the previous reaction (Part D) in 1.2 ml of DMF and 6.5 ml of THF is added 0.17 g of 1-hydroxybenzotriazole. After stirring at room temperature for 19 hr the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 6.25% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.077 g of product. The structure is supported by high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 815. Theory for $C_{44}H_{62}N_8O_7$, 815.4819;

Measured, 815.4848.

Part F.

A mixture of 0.077 g (0.095 mmol) of the cyano peptide, (Part E) 0.076 ml of 1.6 N HCl in Et_2O and 0.05 g of 5% Pd/C catalyst in 150 ml of EtOH is placed on a pressure hydrogenator for 18 hr. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is treated with CH_2Cl_2 and a small amount of aqueous $NaHCO_3$ and mixed well. The aqueous fraction along with some solid material is separated and extracted with EtOAc. The solid material is then removed by filtration, washed once with a couple of drops of H_2O and dried in vacuo to yield crude product A. The organic layers are combined, dried over $MgSO_4$ and concentrated in vacuo to yield crude product B. Crude products A & B are combined and chromatographed over silica gel using 10% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield first 0.028 g of recovered starting cyano peptide followed by 0.024 g (31.0%) of titled product.

Example 8 (3S,5S,6S)-6-[[N^{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[N^{α}-[(2-pyridinyl)ethanoyl]-D-valyl]amino]nonane.

Part A.

To a N_2 covered partial solution of 0.06 g (0.340 mmol) of 2-pyridylacetic acid hydrochloride in 20 ml CH_2Cl_2 is added 0.16 ml (0.907 mmol) of diisopropylethylamine. After stirring at room temperature for 5 min there is added a solution 0.117 g (0.227 mmol) of the amine (Example 7, Part A) in 6 ml of CH_2Cl_2 followed by 0.07 g (0.272 mmol) of 2-chloro-1-methylpyridinium iodide. The mixture is heated at reflux in an oil bath at 50° and then allowed to cool and stand at room temperature for 1 hr. The mixture is then diluted with 20 ml of CH_2Cl_2, washed once with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed over silica gel using 3%MeOH:CH_2Cl_2 containing 0.3% NH_4OH to yield 0.153 g of product contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 635. Theory for $C_{34}H_{63}N_4O_5Si$, 635.4567; Measured, 635.4602.

Part B.

By the general procedure C for Boc group removal, 0.151 g (0.238 mmol) of protected peptide (Part A) yields 0.136 g of the crude free

amine. The amine is then coupled (procedure B) with Boc(tosyl)-histidine and chromatographed with 3% MeOH:CH_2Cl_2 containing 0.3% NH_4OH to yield 0.193 g of coupled peptide contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 926. Theory for $C_{47}H_{76}N_7O_8SSi$, 926.5245; Measured, 926.5263.

Part C.

According to the general procedure C for Boc group removal, 0.193 g of the protected peptide mixture from the previous reaction (Part B) yields 0.148 g of the crude free amine. The amine is then coupled (procedure B) with Boc phenylalanine and chromatographed with 4% MeOH:CH_2Cl_2 containing 4% NH_4OH to yield 0.096 g of the coupled peptide. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 959. Theory for $C_{50}H_{71}N_8O_9S$, 959.5064; Measured, 959.5059.

Part D.

To a solution of 0.089 g (0.0928 mmol) of the tosyl protected peptide (Part C) in 0.9 ml of DMF and 5.0 ml of THF is added 0.13 g of 1-hydroxybenzotriazole. After stirring for 21 hrs the solution is concentrated in vacuo. The residue chromatographed over silica gel using 7% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.066 g (88.3%) of titled product. The structure is supported by high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 805. Theory for $C_{43}H_{65}N_8O_7$, 805.4976; Measured, 805.4983.

Example 9 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]nonane.

Part A.

To a nitrogen covered ice-bath cooled solution of 0.20 g (0.480 mmol of the amine of Example 3 (Part A) and 0.17 ml (1.20 mmol) of triethylamine in 9 ml of THF is added 0.16 ml (1.20 mmol) of isobutylchloroformate. The ice is allowed to melt and the reaction mixture is warmed and is allowed to stir at room temperature. After 22.5 hours the reaction is poured into ice water and extracted three times with methylene chloride. The combined extracts are washed with

dilute brine, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed on a 200 ml silica gel column (elution with 10% ethyl acetate:hexane), 4.8 ml fractions are collected. Fractions 86-140 were combined to yield 0.218 g (87.9%) of the urethane. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m^+H]^+$ at m/z 517. Theory for $C_{27}H_{57}N_2O_5Si$; 517.4036; Measured, 517.4031.

Part B.

By the general procedure F for Boc group removal 0.218 g (0.421 mmol) of the Boc peptide (Part A) yields 0.164 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1.25% MeOH:methylene chloride containing 0.125% NH_4OH to yield 0.293 g (86.1%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m^+H]^+$ at m/z 808; Theory for $C_{40}H_{70}N_5O_8SSi$, 808.4714; Measured, 808.4722.

Part C.

By the general procedure F for Boc group removal 0.10 g (0.124 mmol) of the Boc peptide (Part B) yields 0.084 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenyl-alanine and chromatographed using 3% MeOH:methylene chloride containing 0.3 % NH_4OH to yield 0.096 g (92.0%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[M\cdot+H]^+$ at m/z 841; theory for $C_{43}H_{65}N_6O_9S$, 841.4533; Measured, 841.4528.

Part D.

To a nitrogen covered solution of 0.096 g (0.114 mmol) of the tosyl peptide (Part C) in 1.1 ml of DMF and 5.9 ml of THF is added 0.16 g (1.16 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 22 hours and then concentrated in vacuo. The residue is chromatographed over silica gel using 4% MeOH:CH_2Cl_2 containing 0.4% NH_4OH to yield 0.059 g (75.3%) of titled product. The structure is supported by high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 687; theory for $C_{36}H_{59}N_6O_7$, 687.4445; Measured, 687.4402.

Example 10 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenyl-

alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(isopropylamino)carbonyl]amino]nonane.

Part A.

A N_2 covered solution of 0.10 g (0.240 mmol) of the amine of Example 3 (Part A) and 0.026 ml (0.264 mmol) of isopropylisocyanate in 2 ml of THF is heated at 55° for 2 hr and then concentrated in vacuo. The latter residue and 0.062 g of a residue from a previous 0.120 mmol run are combined and chromatographed on a 150 ml silica gel column (elution with 1% MeOH:CH_2Cl_2) and 5.0 ml fractions are collected. Fractions 131-168 are combined to yield 0.162 g (89.7%) of the urea. The structure is supported by NMR and mass spec.

Part B.

By the general procedure F for Boc group removal 0.164 g (0.327 mmol) of the Boc peptide (Part A) yields 0.148 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1.5% MeOH:CH_2Cl_2 containing 0.15% NH_4OH to yield 0.239 g of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 793.

Part C.

By the general procedure F for Boc group removal 0.10 g (0.126 mmol) of the Boc peptide (Part B) yields 0.08 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenyl-alanine and chromatographed using 3.75% MeOH:CH_2Cl_2 containing 0.375% NH_4OH to yield 0.059 g(56.7%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 826.

Part D.

To a N_2 solution of 0.059 g (0.0714 mmol) of the tosyl peptide (Part C) in 0.7 ml of DMF and 3.6 ml of THF is added 0.097 g (0.714 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 18.5 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 6.25% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.044 g (91.7%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 672; theory for $C_{35}H_{58}N_7O_6$, 672.4448; Measured, 672.4431.

Example 11 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenyl-

alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(methoxyamino)carbonyl]amino]nonane.

Part A.

To a N_2 covered ice bath cooled solution of 0.2 g (0.449 mmol) of the acid (Compound A-1, Chart A) and 0.07 ml (?.493 mmol) of triethylamine in 2.8 ml of acetone and 0.22 ml of water is added 0.064 ml (0.493 mmol) of isobutylchloroformate. After stirring in the cold for 40 min there is added a solution of 0.15 g of sodium azide in 0.8 ml of water over 1.5 min. The mixture is then stirred in the cold for 2 hr 20 min, mixed with 10 ml of ice water and extracted three times with cold EtOAc. The combined extracts are washed once with cold brine, dried over $MgSO_4$ and concentrated in vacuo. The residue is concentrated two additional times from toluene. A solution of the residue in 2 ml of THF is added to a mixture of 0.11 g (1.35 mmol) of methoxyamine hydrochloride and 0.19 ml (1.35 mmol) of triethylamine in 4 ml of THF. (This mixture had been stirring for 24 hrs prior to the addition). The resulting mixture is stirred at 55° for 2.5 hrs, at room temperature for 16 hrs and then concentrated in vacuo. A solution of the residue in CH_2Cl_2 is washed once with water and dilute brine, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed on a 150 ml silica gel column (eluting with 1% MeOH:CH_2Cl_2) and 5.1 ml fractions are collected. Fractions 131-176 are combined to yield 0.156 g (70.9%) of the urea. The product is compared (NMR, TLC) with material prepared from a previous run, the structure of which is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 490; theory for $C_{24}H_{52}N_3O_5Si$, 490.3676; Measured, 490.3688.

Part B.

By the general procedure F for Boc group removal 0.219 g (0.447 mmol) of the Boc peptide (Part A) yielded 0.176 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 2% MeOH:CH_2Cl_2 containing 0.2% NH_4OH to yield 0.294 g (84.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 781.

Part C.

By the general procedure F for Boc group removal 0.10 g (0.128

mmol) of the Boc peptide (Part B) yields 0.099 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 4% MeOH:CH_2Cl_2 containing 0.4% NH_4OH to yield 0.079 g (75.8%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 814.

Part D.

To a N_2 covered solution of 0.079 g (0.0971 mmol) of the tosyl peptide (Part C) in 1.0 ml of DMF and 5.0 ml of THF is added 0.13 g (0.962 mmol) of 1-hydroxybenzotriazole. The solution was stirred at room temperature for 24 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 7.0% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.058 g (90.5%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 660; theory for $C_{34}H_{54}N_7O_7$, 660.4084; Measured, 660.4080.

Example 12 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(propylamino)thiocarbonyl]amino]nonane.

Part A.

A N_2 covered solution of 0.10 g (0.240 mmol) of the amine of Example 3 (Part A) and 0.027 g (0.264 mmol) of propylisothiocyanate in 2 ml of dioxane is stirred at 55° for 2 hr, at 75° for 2.25 hr and then allowed to stand at room temperature for 3 days. The reaction mixture is concentrated in vacuo and the residue is chromatographed over a 100 ml silica gel column (elution with 10% EtOAc:hexane) and 5.2 ml fractions are collected. Fractions 60-102 are combined to yield 0.089 g (71.6%) of the thiourea. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 517.

Part B.

By the general procedure F for Boc group removal 0.089 g (0.172 mmol) of the Boc peptide (Part A) yields 0.071 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosylhistidine and chromatographed using 1% MeOH:CH_2Cl_2 containing 0.1% NH_4OH to yield 0.121 g (86.9%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 809.

Part C.

By the general procedure F for Boc group removal, 0.121 g (0.150 mmol) of the Boc peptide (Part B) yields 0.100 g of product as a two part mixture. This material is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed over a 150 ml silica gel column (elution with 0.67% MeOH:CH_2Cl_2 containing 0.67% NH_4OH to fraction 192, then 1.25% MeOH:CH_2Cl_2 containing 0.125% NH_4OH to fraction 340, then 3% MeOH:CH_2Cl_2 containing 0.3% NH_4OH). There are collected 5.3 ml fractions to fraction 340 and then two 500 ml fractions are collected. Fractions 160-230 are combined to yield 0.043 g (30.0%) of coupled product A which still retained the tert-butyldimethylsilyl (TBDMS) protecting group. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 956.

The first of the two 500 ml fractions yields 0.051 g of the coupled product B which lacked the tert-butyldimethylsilyl protecting group. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 842.

Part D.

To a N_2 covered solution of 0.051 g (0.0606 mmol) of the tosyl peptide (Product B, Part C) in 0.6 ml of DMF and 3.0 ml of THF is added 0.082 g (0.606 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 17.5 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 4% MeOH:CH_2Cl_2 containing 0.4% NH_4OH to yield 0.025 g (60.0%) of titled product. The structure is supported by high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 688; theory for $C_{35}H_{58}N_7O_5S$, 688.4220; Measured, 688.4210.

Example 13 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-3-[(N,N-dimethylsulfamoyl)amino]-5-hydroxynonane.

Part A.

A N_2 covered solution of 0.226 g (0.542 mmol) of the amine of Example 3 (Part A) and 0.029 ml (0.271 mmol) of dimethylsulfamoyl chloride in 5 ml of THF is heated at 70° for 46 hrs and then allowed to cool and concentrated in vacuo. The reside is chromatographed over a 150 ml silica gel column (elution with 1% MeOH:CH_2Cl_2) and 5.3

ml fractions are collected. Fractions 127-152 are combined to yield 0.088 g (62%) of the sulfonamide. The structure of product from a previous run is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 524.

Part B.

By the general procedure F for Boc group removal 0.134 g (0.256 mmol) of the Boc peptide (Part A) yielded 0.106 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1% MeOH:CH_2Cl_2 containing 0.1% NH_4OH to yield 0.160 g (76.7%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 815.

Part C.

By the general procedure F for Boc group removal 0.160 g (0.196 mmol) of the Boc peptide (Part B) yields 0.140 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 2.5% MeOH:CH_2Cl_2 containing 0.25% NH_4OH to yield 0.130 g (78.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 848.

Part D.

To a N_2 covered solution of 0.130 g (0.153 mmol) of the tosyl peptide (Part C) in 1.6 ml of DMF and 7.9 ml of THF is added 0.21 g (0.153 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 25 hrs and then concentrated in vacuo. The residue is chromatographed over a 150 ml silica gel column using 4% MeOH:CH_2Cl_2 containing 0.4% NH_4OH to fraction 174 and then switching to 5% MeOH:CH_2Cl_2 containing 0.5% NH_4OH (fraction volumes were 5.3 ml) to yield 0.087 g (81.9%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 694; theory for $C_{33}H_{56}N_7O_7S$, 694.3962; Measured, 694.3971.

Example 14 (3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-3-[(ethanesulfonyl)amino]-2,8-dimethyl-5-hydroxynonane.

Part A.

A N_2 covered ice bath cooled solution of 0.1 g (0.240 mmol) of the amine of Example 3 (Part A) and 0.037 ml (0.264 mmol) of tri-

ethylamine in 2 ml of CH_2Cl_2 is added 0.025 ml (0.264 mmol) of ethane sulfonyl chloride. The cold bath is removed and the mixture is stirred at room temperature for 46.5 hrs. The reaction mixture is then diluted with CH_2Cl_2 washed once with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed over a 50 ml silica gel column (elution with 0.75% MeOH:CH_2Cl_2) and 4.8 ml fractions are collected. Fractions 60-86 are combined to yield 0.098 g (80.2%) of the sulfonamide. The structure of the product prepared from another run is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 509.

Part B.

By the general procedure F for Boc group removal 0.078 g (0.153 mmol) of the Boc peptide (Part A) yields 0.059 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1% MeOH:CH_2Cl_2 containing 0.1% NH_4OH to yield 0.097 g (79.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 800.

Part C.

By the general procedure F for Boc group removal 0.117 g (0.146 mmol) of the Boc peptide (Part B) yields 0.101 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 2.5% MeOH:CH_2Cl_2 containing 0.25% NH_4OH to yield 0.112 g (92.1%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 833.

Part D.

To a N_2 covered solution of 0.112 g (0.134 mmol) of the tosyl peptide (Part C) in 1.4 ml of DMF and 6.9 ml of THF is added 0.18 g (1.34 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 22 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 5% MeOH:CH_2Cl_2 containing 0.5% NH_4OH to yield 0.086 g (94.5%) of titled product. The structure is supported by high resolution FAB mass spec.

Found: $[m\cdot + H]^+$ at m/z 679; theory for $C_{33}H_{55}N_6O_7S$, 679.3861; Measured, 679.3861.

Preparation 2 N-tert-Butyloxyphenylalanine-p-nitro-phenyl ester (Formula B-2). Refer to Chart B.

A cold solution (0°C) of Boc-Phenylalanine (17.5 g.), p-nitrophenol (10 g.) and dicyclohexylcarbodiimide (20.7 g.) in 100 ml of ethyl acetate is stirred for one hour. The mixture is filtered and filtrate is washed with water, 10% sodium bicarbonate solution, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo. The residue is triturated with ether and filtered to afford the title product.

Physical characteristics are as follows:

Anal. found: C, 62.37; H, 5.73; N, 7.21.

FAB mass spec.: [m + H] at m/z 367.

Preparation 3 N-tert-Butyloxyphenylalanine-histidine methyl ester (Formula B-3). Refer to Chart B.

A solution of Boc-Phe-p-nitrophenyl ester (2.5 g.) of Preparation 2, His-methyl ester hydrochloride (1.45 g.) and triethylamine (2 ml) in 10 ml of dimethylformamide is stirred at room temperature for 18 hours. The mixture is filtered and filtrate is diluted with ethyl acetate, washed with water, 10% sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate) and concentrated in vacuo to afford the title product.

Physical characteristics are as follows:

Anal. found: C, 60.04; H, 7.04; N, 13.10.

FAB mass spec.: [m + H] at m/z 416.

Preparation 4 N-tert-Butyloxycarbonylphenylalanine-histidine(tosyl)-methyl ester (Formula B-4). Refer to Chart B.

A solution of Boc-Phe-His-OCH_3 (500 mg) of Preparation 3, tosyl chloride (230 mg) and triethylamine (120 mg) in 10 ml of methylene chloride is stirred at room temperature for one hour. The mixture is diluted with methylene chloride (30 ml) and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to afford a white oil. The oil on trituration with hexane gives the white crystalline title product.

Physical characteristics are as follows:

Anal. found: C, 58.94; H, 6.24; N, 9.74; S, 5.62.

FAB mass spec.: [m + H] at m/z 571.

Preparation 5 N-tert-Butyloxycarbonylphenylalanine-histidine(tosyl) (Formula B-5). Refer to Chart B.

A solution of Boc-Phe-His(Tos)-OCH_3 (1 g.) of Preparation 4, lithium hydroxide (210 mg) in 10 ml of tetrahydrofuran:water (9:1) is

stirred at room temperature for 30 min. The mixture is concentrated in vacuo, residual aqueous solution is poured onto ice, acidified with 3 N hydrochloric acid and extracted three times with 50 ml of ether. The ether solution is dried (sodium sulfate) and concentrated in vacuo to afford the title product as an amorphous solid.

Physical characteristics are as follows:

Anal. found: C, 57.63; H, 5.83; N, 9.87.

FAB mass spec.: [m + H] at m/z 557.

Example 15 Boc-Phe-His-Sta-Ile-$NHOCH_3$ (Formula C-5: R is methyl).

Refer to Chart C.

A. Boc-Ile-methylhydroxamate (Formula C-2: R is methyl).

To a solution of Boc Isoleucine (2.66 g.) and methylhydroxylamine hydrochloride (1.16 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2.25 g.) and triethylamine (3.6 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a white solid. Recrystallization from diethyl ether gives the title product.

Physical characteristics are as follows:

M.p.: 119-121°C.

B. Boc-Sta-Ile-$NHOCH_3$ (Formula C-3: R is methyl).

A solution of Boc-Ile-$NHOCH_3$ (260 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), dicyclohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the resulting solution is stirred for 18 hours. The above solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give an oil. The oil is purified by column chromatography on silica using ethyl acetate as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mas spec.: [m + H] at m/z 418.

C. Box-Phe-His(Tos)-Sta-Ile-$NHOCH_3$ (Formula C-4: R is methyl).

A solution of Boc-Sta-Ile-$NHOCH_3$ (100 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (130 mg), diethylcyanophosphonate (40 µl) and triethylamine (50 µl). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving 150 mg of crude solid. The solid is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 856.

D. Boc-Phe-His-Sta-Ile-$NHOCH_3$ (Formula C-5: R is methyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-$NHOCH_3$ (85 mg) of Part C and 1-hydroxybenzotriazole (40 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give 130 mg of crude oil. The oil on trituration with anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 702.

Example 16 Boc-Phe-His-Sta-Ile-$NHOCH_2$-phenyl (Formula C-5: R is benzyl). Refer to Chart C.

A. Boc-Ile-Benzylhydroxamate (Formula C-2: R is benzyl).

To a solution of Boc-Ile (2.26 g.) and benzylhydroxylamine hydrochloride (2 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2 g.) and triethylamine (3.5 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude oil. The oil is purified by column chromatography using 35% ethyl acetate/hexane as an eluent. This affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 337.

B. Boc-Sta-Ile-$NHOCH_2$-phenyl (Formula C-3: R is benzyl).

A solution of Boc-Ile-$NHOCH_2$-phenyl (200 mg) of Part A in 5 ml of 50% trifluoroacetic acid/methylene chloride is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added diethylcyanophosphonate (100 µl), Boc-Sta (165 mg), triethylamine (200 µl) and the resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 15 ml of methylene chloride and washed with water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give a crude yellow amorphous solid. This solid is purified by column chromatography on silica gel using 50% ethyl acetate/hexane as eluent. This affords a yellow solid title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 494.

C. Boc-Phe-His(Tos)-Sta-Ile-$NHOCH_2$-phenyl (Formula C-4: R is benzyl).

A solution of Boc-Sta-Ile-$NHOCH_2$-phenyl (100 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and the residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (110 mg), diethylcyanophosphonate (40 µl) and triethylamine (50 µl). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving a crude yellow oil. The oil is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 932.

D. Boc-Phe-His-Sta-Ile-$NHOCH_2$-phenyl (Formula C-5: R is benzyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-$NHOCH_2$-phenyl (80 mg) of Part C and 1-hydroxybenzotriazole (40 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and

concentrated in vacuo to give a crude oil. The oil on trituration with anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 778.

Example 17 Boc-Phe-His-Sta-Ile-NHO-phenyl (Formula C-5: R is phenyl). Refer to Chart C.

A. Boc-Ile-phenylhydroxamate (Formula C-2: R is phenyl).

To a solution of Boc-Ile (2 g.) and phenylhydroxylamine hydrochloride (1.88 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2 g.) and triethylamine (3.4 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil. The oil is purified by column chromatography on silica gel using 35% ethyl acetate/hexane as an eluent to afford white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 323.

B. Boc-Sta-Ile-NHO-phenyl (Formula C-3: R is phenyl).

A solution of Boc-Ile-NHO-phenyl (322 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), dicyclohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the resulting solution is stirred for 18 hours. The solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give an oil. The oil is purified by column chromatography on silica gel using 50% ethyl acetate/hexane as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 418.

C. Boc-Phe-His(Tos)-Sta-Ile-NHO-phenyl (Formula C-4: R is phenyl).

A solution of Boc-Sta-Ile-NHO-phenyl (125 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The

solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (140 mg), diethylcyanophosphonate (40 μl) and triethylamine (50 μl). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving a crude oil. The oil is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 918.

D. Boc-Phe-His-Sta-Ile-NHO-phenyl (Formula C-5: R is phenyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-NHO-phenyl (75 mg) of Part C and 1-hydroxybenzotriazole (75 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride, dried (sodium sulfate) and concentrated in vacuo to give a crude oil. The oil on trituration with anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 764.

Example 18 Boc-Phe-His-Sta-Ile-NHOEt (Formula C-5: R is ethyl). Refer to Chart C.

A. Boc-Ile-ethylhydroxamate (Formula C-2: R is ethyl).

To a solution of Boc-Ile (2 g.) and ethylhydroxylamine hydrochloride (1.35 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2 g.) and triethylamine (3.4 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with methylene chloride (50 ml), washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil. The oil on trituration with ether/-hexane gives white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 278.

B. Boc-Sta-Ile-$NHOC_2H_5$ (Formula C-3: R is ethyl).

A solution of Boc-Ile-$NHOC_2H_5$ (275 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room

temperature for 30 min. The solution is then concentrated in vacuo and the residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), dicyclohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the resulting solution is stirred for 18 hours. The solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give an oil. The oil is purified by column chromatography on silica gel using 50% ethyl acetate/hexane as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 432.

C. Boc-Phe-His(Tos)-Sta-Ile-$NHOC_2H_5$ (Formula C-4: R is ethyl).

A solution of Boc-Sta-Ile-$NHOC_2H_5$ (215 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (278 mg), diethylcyanophosphonate (80 μl) and triethylamine (100 μl). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving an oil. The oil is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 870.

D. Boc-Phe-His-Sta-Ile-$NHOC_2H_5$ (Formula C-5: R is ethyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-$NHOC_2H_5$ (100 mg) of Part C and 1-hydroxybenzotriazole (100 mg) in 5 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give a crude oil. The oil on trituration with anhydrous ether gives the title product.

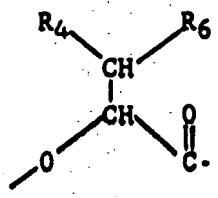
Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 716.

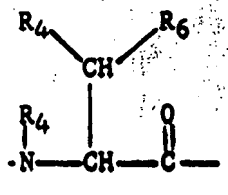
FORMULAE

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}V \qquad I$$

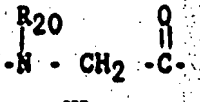
$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{121}\text{-}H_{131}\text{-}I_{14}\text{-}Z \qquad II$$



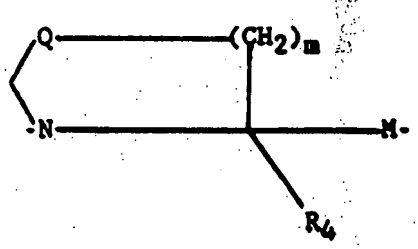
XL_1



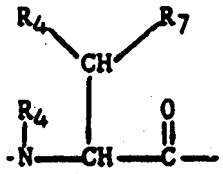
XL_2



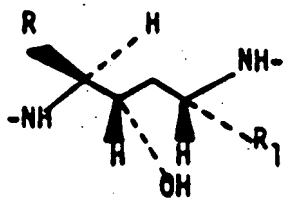
XL_{2a}



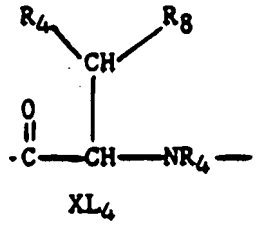
XL_3



XL_3



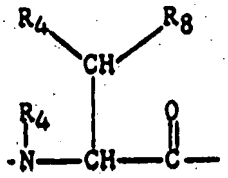
XL_a



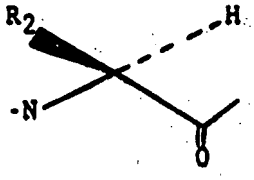
XL_4

XL_{4a}

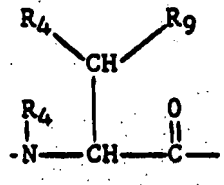
FORMULAE (Continued)



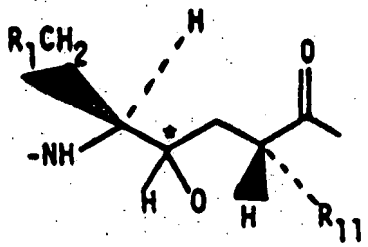
XL_{41}



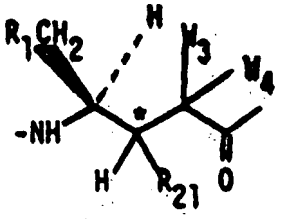
XL_{4a1}



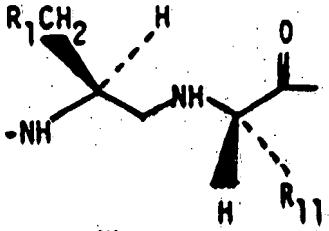
XL_5



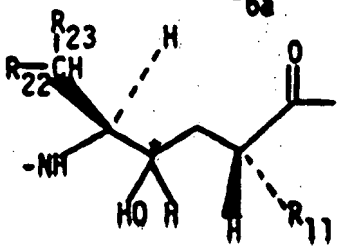
XL_6



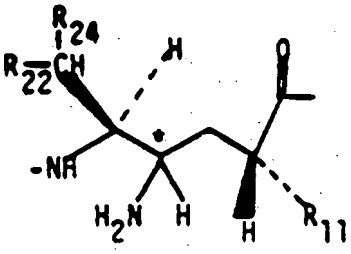
XL_{6a}



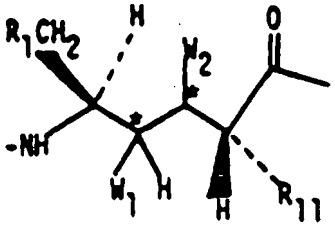
XL_{6b}



XL_{6c}

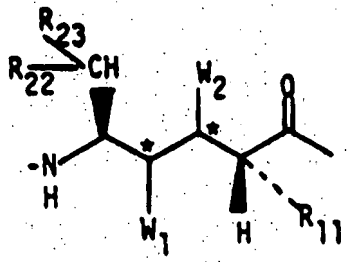


XL_{6d}

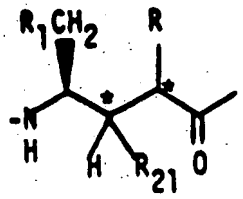


XL_{6e}

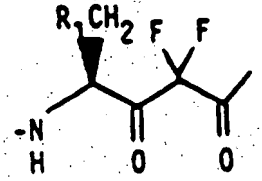
FORMULAE (Continued)



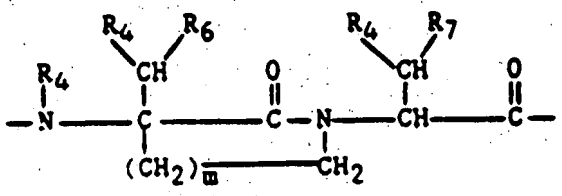
XL_{6f}



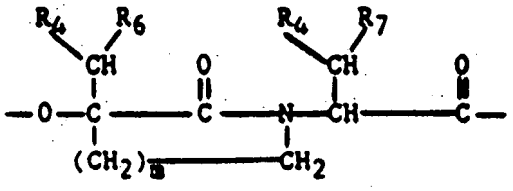
XL_{6g}



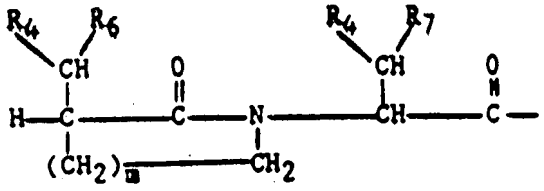
XL_{6h}



XL_7



XL_{7a}



XL_{7b}

CHART A

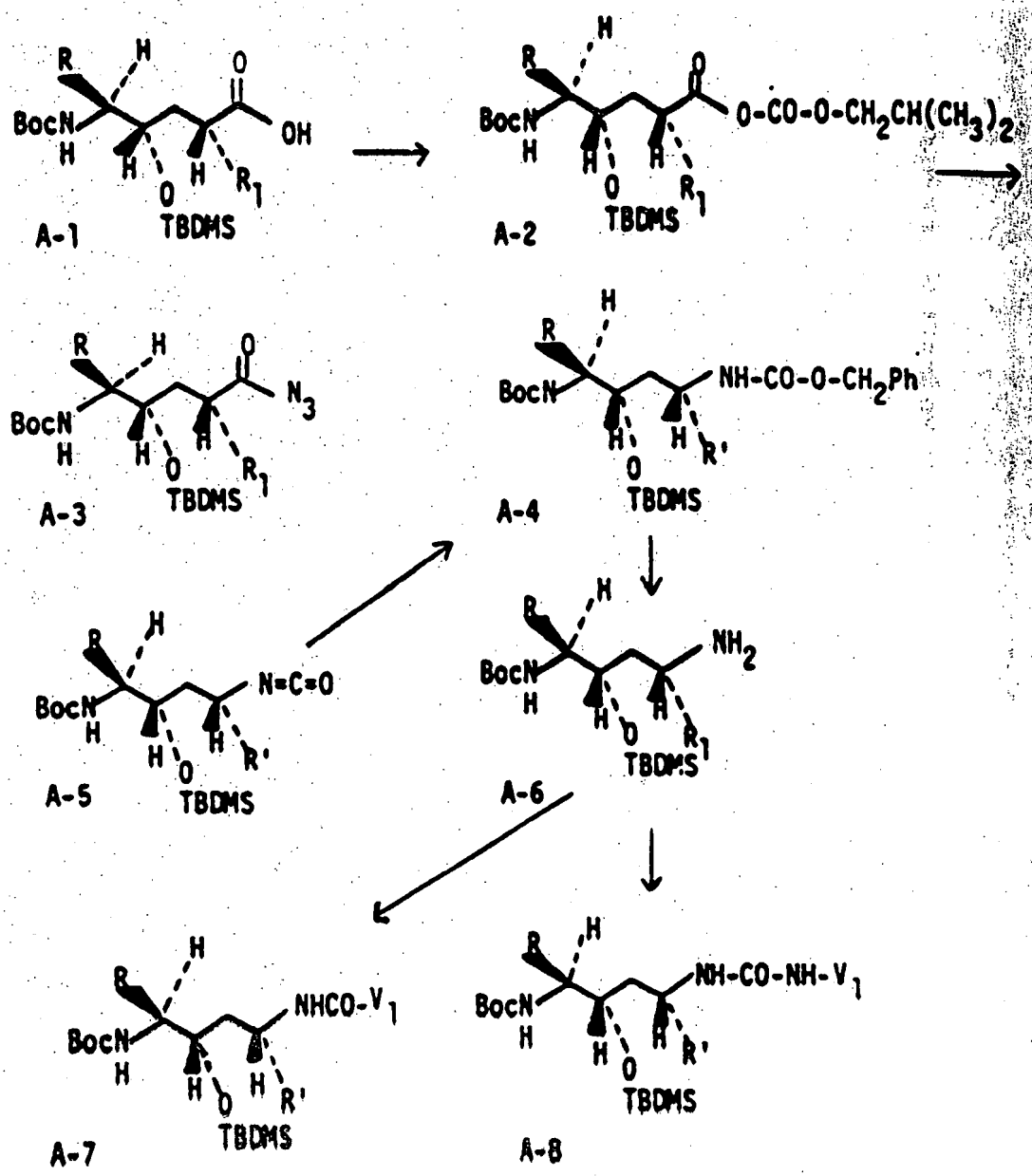


CHART A (continued)

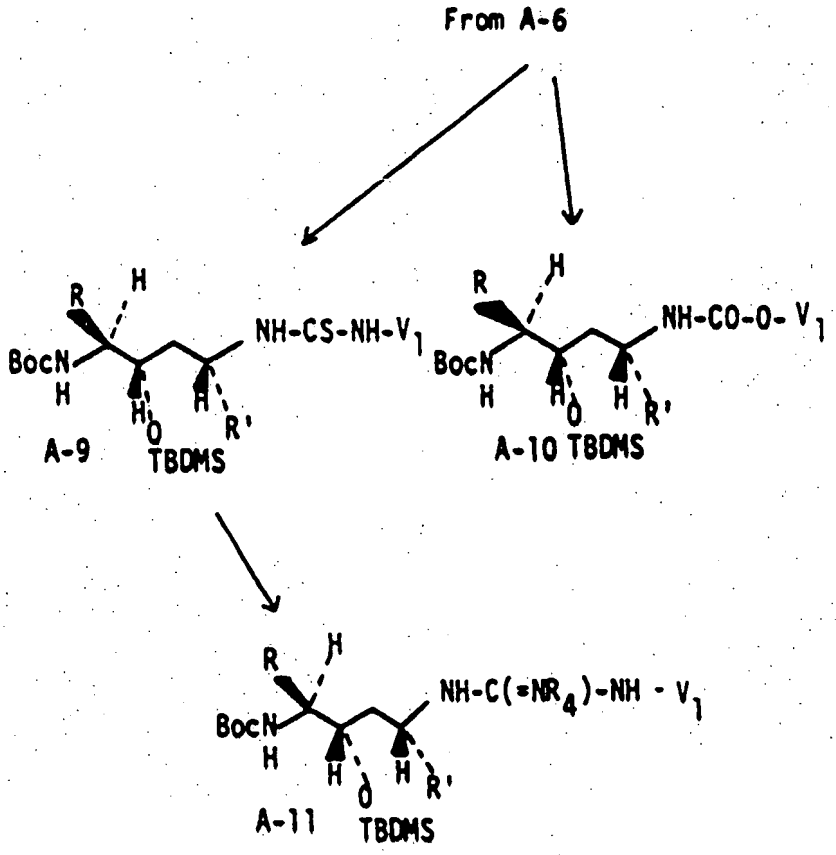


CHART B

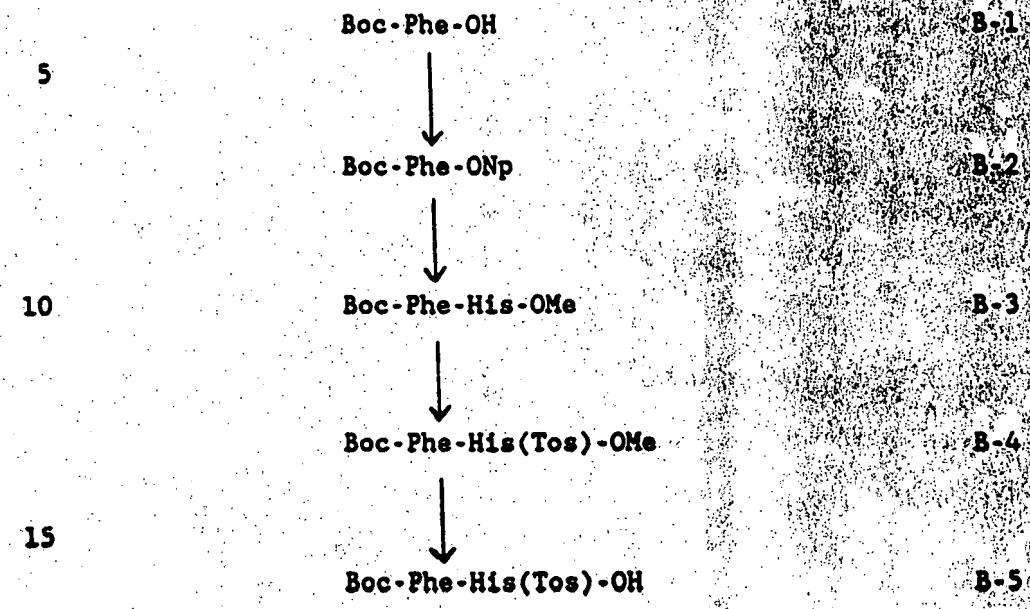
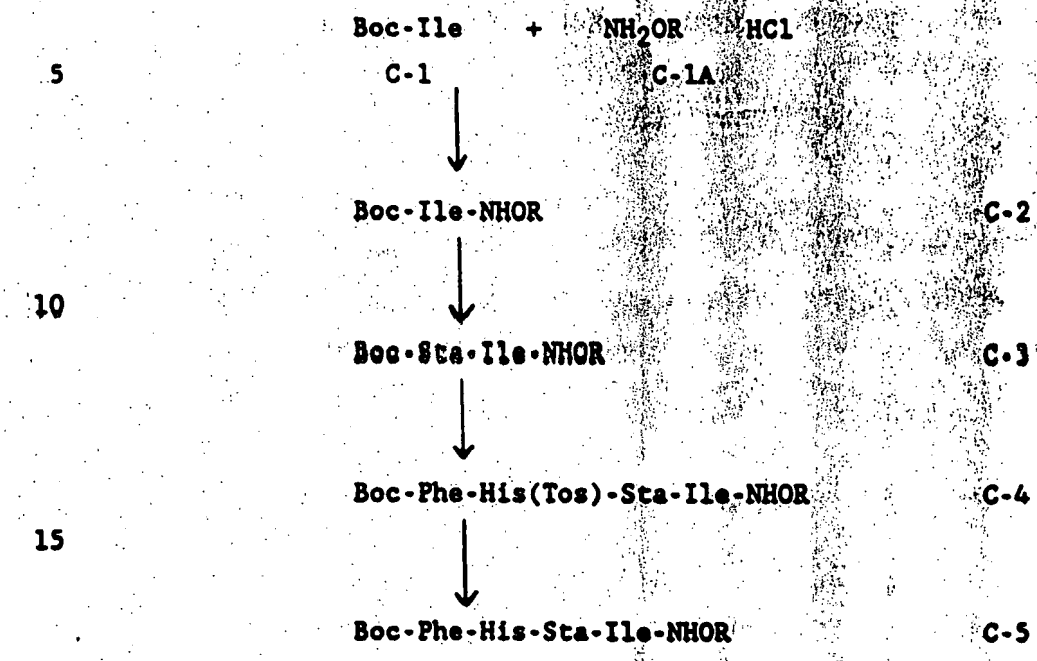


CHART C



CLAIMS

1. A renin inhibitory peptide having a noncleavable transition state insert corresponding to the 10,11-position of the renin substrate (angiotensinogen) and having a moiety of the formula V, wherein V is

(a) $-C(=Y)-G_{12}-H_{13}-Z$,

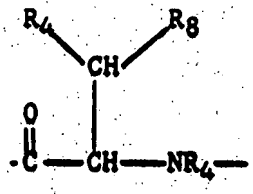
(b) $-W$,

(c) $-G_{12}-H_{13}-W$, or

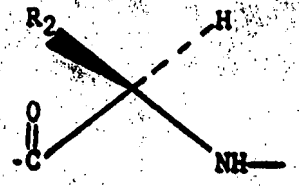
(d) $-G_{121}-H_{131}-I_{14}-Z$;

corresponding to positions 12 to 14 of the renin substrate;

wherein G_{12} is absent or a divalent moiety of the formula XL_4 or XL_{4a}

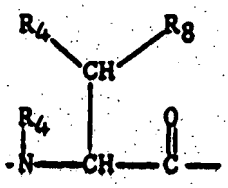


XL_4

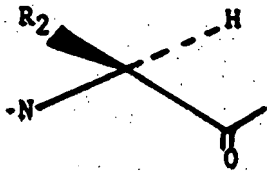


XL_{4a}

wherein G_{121} is absent or a divalent moiety of the formula XL_{41} or XL_{4a1}

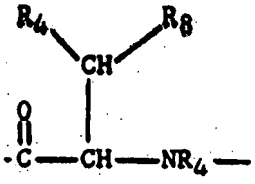


XL_{41}



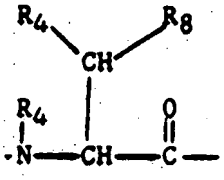
XL_{4a1}

wherein H_{13} is absent or a divalent moiety of the formula XL_4



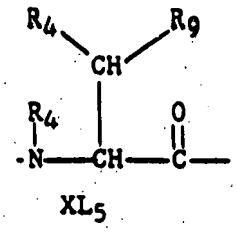
XL_4

wherein H_{131} is absent or a divalent moiety of the formula XL_{41}



XL_{41}

wherein I_{14} is absent or a divalent moiety of the formula XL_5



XL_5

wherein W is

(a) R_{14},

(b) $-C(=Y)-CH_2-Y-R_5$,

(c) $-C(=Y)-YR_5$,

(d) $-C(=Y)(CH_2)_n-R_5$,

(e) $-C(=Y)-(CH_2)_nN-(R_4)_2$,

(f) $-SO_2R_5$,

(g) $-SO_2N(R_4)_2$,

(h) $-C(=Y)(CH_2)_2-SO_2R_5$,

(i) $-C(=Y)-Y-(CH_2)_2-SO_2-R_5$,

(j) $-C(=Y)-NR_4-O-R_5$,

(k) $-C(=NCN)NHR_4$, or

(l) $-C(=Y)(CH_2)_qC(=Y)YR_4$;

wherein each occurrence of Y may be the same or different and Y is

(a) -O-,

(b) -S-, or

(c) $-NR_4-$;

wherein Z is

(a) $-O-R_{10}$,

(b) $-N(R_4)R_{14}$,

(c) $-C_4-C_8$cyclic amino, or

(d) $-N(R_{10})(OR_{14})$;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,

(c) C_1-C_5alkyl,

(d) C_3-C_7cycloalkyl,

(e) aryl,

(f) -Het,

(g) C_1-C_3alkoxy, or

(h) C_1-C_3alkylthio;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1-C_5alkyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het,

(e) 5-oxo-2-pyrrolidinyl, or

(f) $-C(CH_2OH)_3$;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) aryl,

(e) -Het,

(f) guanidinyl C_1-C_3alkyl-,

(g) C_3-C_7cycloalkyl, or

(h) $-(CH_2)_p$-C_3-C_7cycloalkyl;

wherein R_9 is

(a) hydrogen,

(b) hydroxy,

(c) amino C_1-C_4alkyl-, or

(d) guanidinyl-C_1-C_3alkyl-;

wherein R_{10} is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_nR_{16}$,

(d) $-(CH_2)_nR_{17}$,

(e) C_3-C_7cycloalkyl,

(f) a pharmaceutically acceptable cation,

(g) $-(CHR_{25})-CH_2-R_{15}$, or

(h) $-CH_2-(CHR_{12})-R_{15}$;

wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is

(a) aryl,

(b) amino,
(c) mono-, di- or tri-C_1-C_3alkylamino,
(d) -Het,
(e) C_1-C_5alkyl,
(f) C_3-C_7cycloalkyl,
(g) C_2-C_5alkenyl,
(h) C_3-C_7cycloalkenyl,
(i) hydroxy,
(j) C_1-C_3alkoxy,
(k) C_1-C_3alkanoyloxy,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) -COOH,
(o) -CO-O-C_1-C_6alkyl,
(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,
(q) -CO-$NR_{22}R_{26}$,
(r) C_4-C_7cyclic amino,
(s) C_4-C_7cycloalkylamino,
(t) guanidyl,
(u) cyano,
(v) N-cyanoguanidyl,
(w) cyanoamino,
(x) (hydroxy C_2-C_4alkyl)amino,
(y) di-(hydroxy C_2-C_4alkyl)amino, or
(z) -CO-$NR_{22}R_{25}$;

wherein R_{14} is

(a) hydrogen,
(b) C_1-C_{10}alkyl,
(c) -$(CH_2)_n$-R_{18},
(d) -$(CH_2)_n$-R_{19},
(e) -(CHR_{25})-CH_2-R_{15},
(f) -CH_2-(CHR_{12})-R_{15},
(g) (hydroxy C_1-C_8alkyl),
(h) (C_1-C_3alkoxy) C_1-C_8alkyl,
(i) -$(CH_2)_n$-aryl,
(j) -$(CH_2)_n$-Het,
(k) -$(CH_2)_{n+2}$-R_{18}, or
(l) -$(CH_2)_{n+2}$-R_{19};

wherein R_{15} is

(a) hydroxy,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) amino,

(e) mono-, di-, or tri-C_1-C_3alkylamino,

(f) mono- or di-(hydroxy C_2-C_4alkyl)amino,

(g) -Het,

(h) C_1-C_3alkoxy-,

(i) C_1-C_3alkanoyloxy-,

(j) mercapto,

(k) C_1-C_3alkylthio-,

(l) C_1-C_5alkyl,

(m) C_4-C_7cyclic amino,

(n) C_4-C_7cycloalkylamino,

(o) C_2-C_5alkenyloxy, or

(p) C_3-C_7cycloalkenyl;

wherein R_{16} is

(a) aryl,

(b) amino,

(c) mono- or di-C_1-C_3alkylamino,

(d) hydroxy,

(e) C_3-C_7cycloalkyl,

(f) C_4-C_7cyclic amino, or

(g) C_1-C_3alkanoyloxy;

wherein R_{17} is

(a) -Het,

(b) C_2-C_5alkenyl,

(c) C_3-C_7cycloalkenyl,

(d) C_1-C_3alkoxy,

(e) mercapto,

(f) C_1-C_3alkylthio,

(g) -COOH,

(h) -CO-O-C_1-C_6alkyl,

(i) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(j) -CO-$NR_{22}R_{26}$,

(k) tri-C_1-C_3alkylamino,

(l) guanidyl,

(m) cyano,
(n) N-cyanoguanidyl,
(o) (hydroxy C_2-C_4alkyl)amino, or
(p) di-(hydroxy C_2-C_4alkyl)amino;

wherein R_{18} is
(a) amino,
(b) mono-, or di-C_1-C_3alkylamino,
(c) C_4-C_7cyclic amino, or
(d) C_4-C_7cycloalkylamino;

wherein R_{19} is
(a) aryl,
(b) -Het,
(c) tri-C_1-C_3alkylamino,
(d) C_3-C_7cycloalkyl,
(e) C_2-C_5alkenyl,
(f) C_3-C_7cycloalkenyl,
(g) hydroxy,
(h) C_1-C_3alkoxy,
(i) C_1-C_3alkanoyloxy,
(j) mercapto,
(k) C_1-C_3alkylthio,
(l) -COOH,
(m) -CO-O-C_1-C_6alkyl,
(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,
(o) -CO-$NR_{22}R_{26}$,
(p) C_4-C_7cycloalkylamino,
(q) guanidyl,
(r) cyano,
(s) N-cyanoguanidyl,
(t) cyanoamino,
(u) (hydroxy C_2-C_4alkyl)amino,
(v) di-(hydroxy C_2-C_4alkyl)amino,
(w) -SO_3H, or
(x) -CO-$NR_{22}R_{25}$;

wherein R_{22} is
(a) hydrogen, or
(b) C_1-C_3alkyl;

wherein R_{25} is

(a) $-(CH_2)_n-R_{13}$,
(b) hydrogen,
(c) C_1-C_3alkyl, or
(d) phenyl-C_1-C_3alkyl;

wherein R_{26} is
(a) hydrogen,
(b) C_1-C_3alkyl, or
(c) phenyl-C_1-C_3alkyl;

wherein for each occurrence n is independently an integer of zero to five inclusive;

wherein p is zero to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:
(a) C_1-C_3alkyl,
(b) hydroxy,
(c) C_1-C_3alkoxy,
(d) halo,
(e) amino,
(f) mono- or di- C_1-C_3alkylamino,
(g) -CHO,
(h) -COOH,
(i) $COOR_{26}$,
(j) $CONHR_{26}$,
(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) $-N(R_4)-C_1$-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN,
(t) $-CH_2NH_2$,
(u) $COOR_{25}$, or
(v) $CONHR_{25}$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group

consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino, or
(ix) mono- or di- C_1-C_4alkylamino;

or a carboxy-, amino-, or other reactive group-protected form; or a pharmaceutically acceptable acid addition salt thereof.

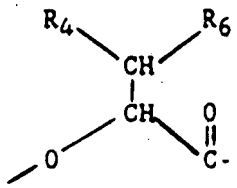
2. A renin inhibitory peptide of claim 1 of the formula I

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}V \qquad I$$

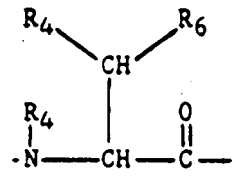
wherein X is

(a) hydrogen,
(b) C_1-C_5alkyl
(c) R_5-O-CH_2-C(O)-,
(d) R_5-CH_2-O-C(O)-,
(e) R_5-O-C(O)-,
(f) R_5-$(CH_2)_n$-C(O)-,
(g) $R_4N(R_4)$-$(CH_2)_n$-C(O),
(h) R_5-SO_2-$(CH_2)_q$-C(O)-, or
(i) R_5-SO_2-$(CH_2)_q$-O-C(O)-;

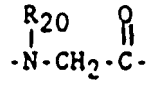
wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, or XL_{2a}



XL_1

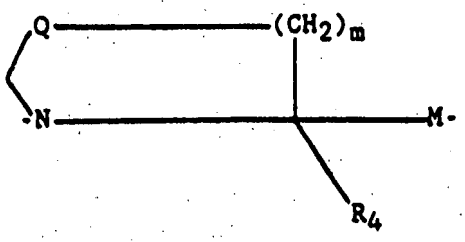


XL_2



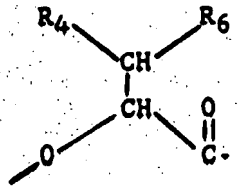
XL_{2a}

wherein B_7 is absent or a divalent moiety of the formula XL_b

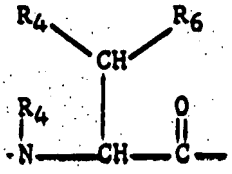


XL_b

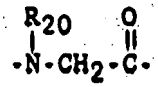
wherein C_8 is absent or a divalent moiety of the formula XL_1, XL_2, or XL_{2a};



XL_1

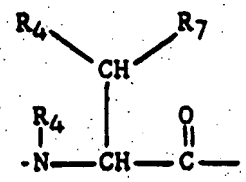


XL_2

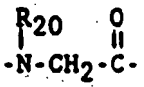


XL_{2a}

wherein D_9 is a divalent moiety of the formula XL_3 or XL_{2a};

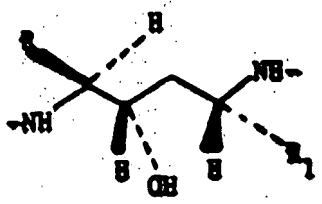


XL_3



XL_{2a}

wherein E_{10}-F_{11} is a divalent moiety of the formula XLa,



XLa

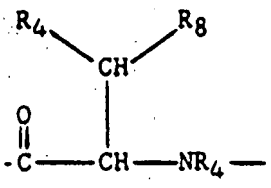
wherein V is

(a) -C(=Y)-G_{12}-H_{13}-Z,

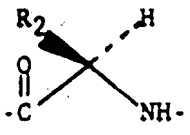
(b) -W, or

(c) -G_{12}-H_{13}-W;

wherein G_{12} is absent or a divalent moiety of the formula XL_4 or XL_{4a}

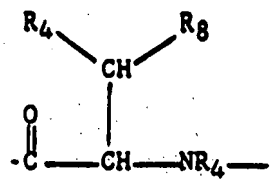


XL_4



XL_{4a}

wherein H_{13} is absent or a divalent moiety of the formula XL_4



XL_4

wherein W is

(a) R_{14},

(b) $-C(=Y)-CH_2-Y-R_5$,

(c) $-C(=Y)-YR_5$,

(d) $-C(=Y)(CH_2)_n-R_5$,

(e) $-C(=Y)-(CH_2)_nN-(R_4)_2$,

(f) $-SO_2R_5$,

(g) $-SO_2N(R_4)_2$,

(h) $-C(=Y)(CH_2)_2-SO_2R_5$,

(i) $-C(=Y)-Y-(CH_2)_2-SO_2-R_5$,

(j) $-C(=Y)-NR_4-O-R_5$,

(k) $-C(=NCN)NHR_4$, or

(l) $-C(=Y)(CH_2)_qC(=Y)YR_4$;

wherein each occurrence of Y may be the same or different and Y is

(a) -O-,

(b) -S-, or

(c) $-NR_4-$;

wherein Z is

(a) $-O-R_{10}$,

(b) $-N(R_4)R_{14}$, or

(c) $-C_4-C_8$ cyclic amino;

wherein R and R_1 are the same or different and are

(a) C_1-C_{10}alkyl,

(b) C_3-C_{10}cycloalkyl,

(c) aryl,

(d) C_1-C_{10} alkyl substituted by one or two

(1) hydroxy,

(2) C_1-C_3 alkoxy,

(3) C_1-C_3 alkylthio,

(4) aryl,

(5) C_3-C_{10} cycloalkyl,

(6) Het,

(7) amino,

(8) mono C_1-C_3 alkylamino,

(9) di C_1-C_3 alkyl and amino.

(e) C_1-C_3alkoxy, or

(f) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,

(c) C_1-C_5alkyl,

(d) C_3-C_7cycloalkyl,

(e) aryl,

(f) -Het,

(g) C_1-C_3alkoxy, or

(h) C_1-C_3alkylthio;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1-C_5alkyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het,

(e) 5-oxo-2-pyrrolidinyl, or

(f) $-C(CH_2OH)_3$;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) amino C_1-C_4alkyl-,
(e) guanidinyl C_1-C_3alkyl-,
(f) aryl,
(g) -Het,
(h) methylthio,
(i) C_3-C_7cycloalkyl, or
(j) amino;

wherein R_8 is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) hydroxy,
(d) aryl,
(e) -Het,
(f) guanidinyl C_1-C_3alkyl-, or
(g) C_3-C_7cycloalkyl;

wherein R_{10} is
(a) hydrogen,
(b) C_1-C_5alkyl,
(c) $-(CH_2)_nR_{16}$,
(d) $-(CH_2)_nR_{17}$,
(e) C_3-C_7cycloalkyl,
(f) a pharmaceutically acceptable cation,
(g) $-(CHR_{25})-CH_2-R_{15}$, or
(h) $-CH_2-(CHR_{12})-R_{15}$;

wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is
(a) aryl,
(b) amino,
(c) mono-, di or tri-C_1-C_3alkylamino,
(d) -Het,
(e) C_1-C_5alkyl
(f) C_3-C_7cycloalkyl,
(g) C_2-C_5alkenyl,
(h) C_3-C_7cycloalkenyl,
(i) hydroxy,
(j) C_1-C_3alkoxy,
(k) C_1-C_3alkanoyloxy,
(l) mercapto,

(m) C_1-C_3alkylthio,

(n) -COOH,

(o) -CO-O-C_1-C_6alkyl,

(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(q) -CO-N$R_{22}R_{26}$;

(r) C_4-C_7cyclic amino,

(s) C_4-C_7cycloalkylamino,

(t) guanidyl,

(u) cyano,

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy C_2-C_4alkyl)amino, or

(y) di-(hydroxyC_2-C_4alkyl)amino;

wherein R_{14} is

(a) hydrogen,

(b) C_1-C_{10}alkyl,

(c) -$(CH_2)_n$-R_{18},

(d) -$(CH_2)_n$-R_{19},

(e) -(CHR_{25})-CH_2-R_{15},

(f) -CH_2-(CHR_{12})-R_{15},

(g) (hydroxy C_1-C_8alkyl), or

(h) (C_1-C_3alkoxy)C_1-C_8alkyl;

wherein R_{15} is

(a) hydroxy,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) amino,

(e) mono-, di-, or tri- C_1-C_3alkylamino,

(f) mono- or di-[hydroxy C_2-C_4alkyl]amino,

(g) -Het,

(h) C_1-C_3alkoxy-,

(i) C_1-C_3alkanoyloxy-,

(j) mercapto,

(k) C_1-C_3alkylthio-,

(l) C_1-C_5alkyl,

(m) C_4-C_7cyclic amino,

(n) C_4-C_7cycloalkylamino,

(o) C_2-C_5alkenyloxy,

(p) C_3-C_7cycloalkenyl;

wherein R_{16} is

(a) aryl,

(b) amino,

(c) mono- or di- C_1-C_3alkylamino,

(d) hydroxy,

(e) C_3-C_7cycloalkyl,

(f) C_4-C_7cyclic amino, or

(g) C_1-C_3alkanoyloxy;

wherein R_{17} is

(a) -Het,

(b) C_2-C_5alkenyl,

(c) C_3-C_7cycloalkenyl,

(d) C_1-C_3alkoxy,

(e) mercapto,

(f) C_1-C_3alkylthio,

(g) -COOH,

(h) -CO-O-C_1-C_6alkyl,

(i) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(j) -CO-$NR_{22}R_{26}$,

(k) tri-C_1-C_3alkylamino,

(l) guanidyl,

(m) cyano,

(n) N-cyanoguanidyl,

(o) (hydroxy C_2-C_4alkyl)amino, or

(p) di-(hydroxy C_2-C_4alkyl)amino;

wherein R_{18} is

(a) amino,

(b) mono-, or di- C_1-C_3alkylamino, or

(c) C_4-C_7cyclic amino;

wherein R_{19} is

(a) aryl,

(b) -Het,

(c) tri-C_1-C_3alkylamino,

(d) C_3-C_7cycloalkyl,

(e) C_2-C_5alkenyl,

(f) C_3-C_7cycloalkenyl,

(g) hydroxy,

(h) C_1-C_3alkoxy,

(i) C_1-C_3alkanoyloxy,

(j) mercapto,

(k) C_1-C_3alkylthio,

(l) -COOH,

(m) -CO-O-C_1-C_6alkyl,

(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(o) -CO-$NR_{22}R_{26}$,

(p) C_4-C_7cycloalkylamino,

(q) guanidyl,

(r) cyano,

(s) N-cyanoguanidyl,

(t) cyanoamino,

(u) (hydroxy C_2-C_4alkyl)amino,

(v) di-(hydroxy C_2-C_4alkyl)amino; or

(w) -SO_3H;

wherein R_{20} is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3alkyl;

wherein R_{25} is -$(CH_2)_n$-R_{13};

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to 2 inclusive;

wherein q is 1 to 5, inclusive;

wherein Q is

(a) -CH_2-,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-; and

wherein M is

(a) -CO-, or

(b) $-CH_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 to the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) $-N(R_4)$-C_1-C_3alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl C_1-C_4alkyl-,

(viii) amino, and

(ix) mono- or di-C_1-C_4alkylamino;

with the overall provisos that

(1) R_{16} or R_{17} is an amino-containing substituent, hydroxy, mercapto, or -Het bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusive;

(2) R_{18} or R_{19} is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

(3) R_{12} is $-(CH_2)_n-R_{13}$ and n is zero and both R_{13} and R_{15} are oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

(4) when R_{12} is $-(CH_2)_n-R_{13}$ and n is zero, then R_{13} and R_{15} cannot both be -COOH;

(5) R_{25} is $-(CH_2)_n-R_{13}$ and n is zero only when R_{13} is other than a primary or secondary nitrogen-containing group hydroxy or mercapto group or when R_4 of $-N(R_4)R_{14}$ is other than hydrogen;

(6) R_{17} or R_{19} is -COOH only when n for that moiety is other than zero;

or a carboxy-, amino-, or other reactive group-protected form or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of claim 2 selected from the group consisting of:

(3S,5S,6S)-3-(Benzyloxycarbonylamino)-6-[[N^{α}-[N^{α}-(t-butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane;

(3S,5S,6S)-3-Amino-6-[[N^{α}-[N^{α}-(t-butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane;

(3S,5S,6S)-6-[[N_{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isopropoxycarbonyl)amino]-nonane;

(3S,5S,6S)-6-[[N_{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histid-yl]amino]-2,8-dimethyl-5-hydroxy-3-[(3-methyl-1-oxybutyl)-amino]-nonane;

(3S,5S,6S)-3-[[N_{α}-(Benzyloxycarbonyl)-D-valyl)]amino]-6-[[N_{α}-[N^{α}-(t-butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane;

(3S,5S,6S)-6-[[N_a[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histid-yl]amino]-2,8-dimethyl-5-hydroxy-3-[(D-valyl)amino]nonane;

(3S,5S,6S)-3-[[N^{α}-[(3-Aminomethyl)benzoyl]-D-valyl]amino]-6-[[N^{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane;

(3S,5S,6S)-6-[[N^{α}[N^{α}-(t-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[N^{a}-[(2-pyridinyl)ethanoyl-D-valyl]amino]nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]-nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(isopropylamino)carbonyl]-amino]nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(methoxyamino)carbonyl]-amino]nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(propylamino)thiocarbonyl]amino]nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-3-[(N,N-dimethylsulfamoyl)amino]-5-hydroxynonane; and

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-3-[(ethanesulfonyl)amino]-2,8-dimethyl-5-hydroxy-nonane.

4. A compound of Claim 2, wherein V is W, W is -C(=Y)-YR_5 or-C(=Y)-NR_4-O-R_5, and Y is -O- or -S-.

5. A compound of Claim 4 selected from

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]-nonane;

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(isopropylamino)carbonyl]-amino]nonane; and

(3S,5S,6S)-6-[[N^{α}-[N^{α}-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-

histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[[(methoxyamino)carbonyl]-amino]nonane.

6. A renin inhibitory peptide of claim 1 of the formula II

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{121}\text{-}H_{131}\text{-}I_{14}\text{-}Z \qquad II$$

wherein X is

(a) hydrogen,

(b) C_1-C_5alkyl

(c) R_5-O-CH_2-C(O)-,

(d) R_5-CH_2-O-C(O)-,

(e) R_5-O-C(O)-,

(f) R_5-$(CH_2)_n$-C(O)-,

(g) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

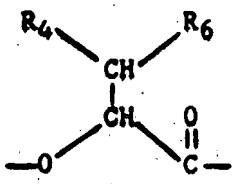
(h) R_5-SO_2-$(CH_2)_q$-C(O)-,

(i) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

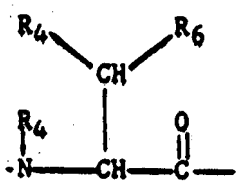
(j) R_6-$(CH_2)_t$-C(O)-, or

(k) $[R_6\text{-}(CH_2)_n]_2CH$-C(O)-;

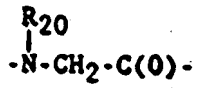
wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, or XL_{2a}



XL_1

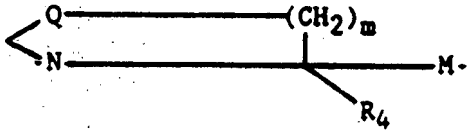


XL_2



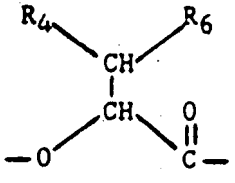
XL_{2a}

wherein B_7 is absent or a divalent moiety of the formula XL_b

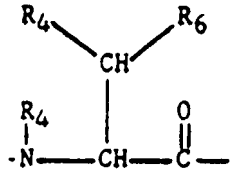


XL_b

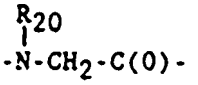
wherein C_8 is absent or a divalent moiety of the formula XL_1, XL_2 or XL_{2a}



XL_1

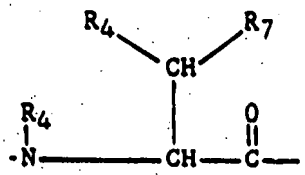


XL_2

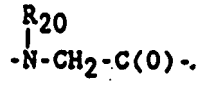


XL_{2a}

wherein D_9 is a divalent moiety of the formula XL_3 or XL_{2a}

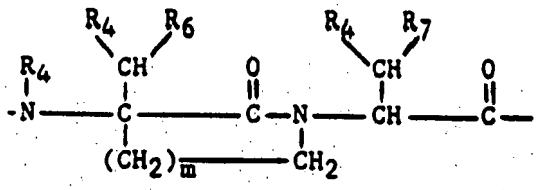


XL_3

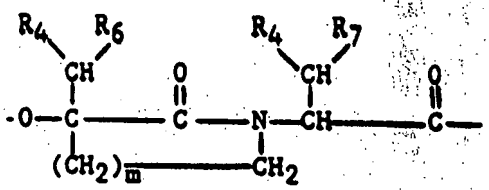


XL_{2a}

or wherein C_8-D_9 is a divalent moiety of the formula XL_7 or XL_{7a},

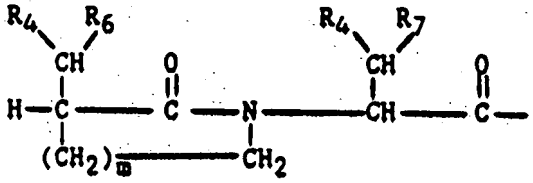


XL_7



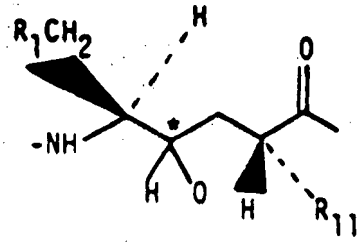
XL_{7a}

or wherein C_8-D_9 is a monovalent moiety of the formula XL_{7b} when X, A_6, and B_7 are all absent;

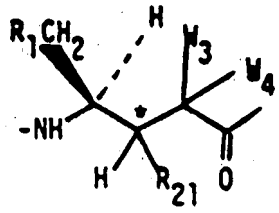


XL_{7b}

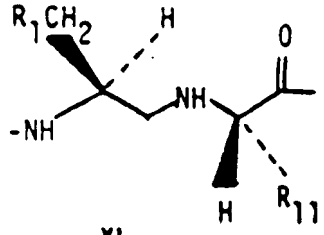
wherein E_{10}-F_{11} is a divalent moiety of the formula XL_6, XL_{6a}, XL_{6b}, XL_{6c}, XL_{6d}, XL_{6e}, XL_{6f}, XL_{6g} or XL_{6h};



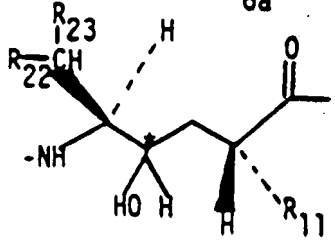
XL_6



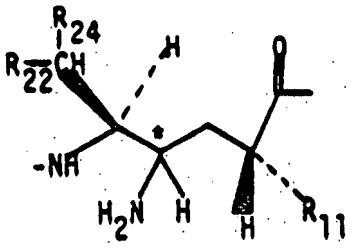
XL_{6a}



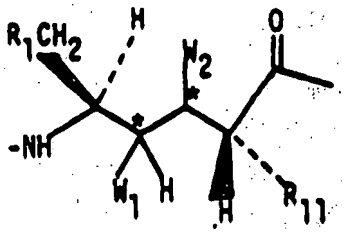
XL_{6b}



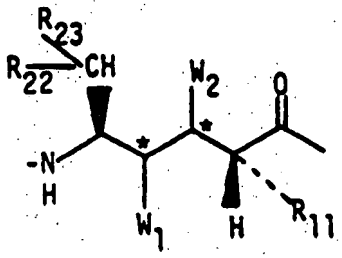
XL_{6c}



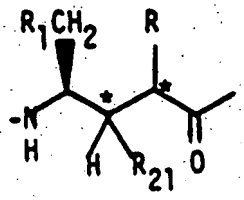
XL_{6d}



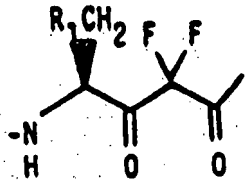
XL_{6e}



XL_{6f}



XL_{6g}



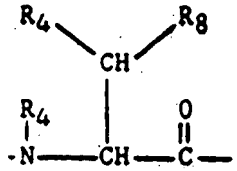
XL_{6h}

wherein * indicates an asymmetric center which is either in the R or S configuration;

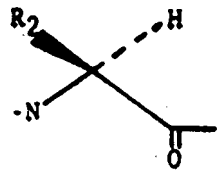
wherein W_1 and W_2 are -OH or $-NH_2$;

wherein W_3 and W_4 are -H or -F;

wherein G_{121} is absent or a divalent moiety of the formula XL_{41} or XL_{4a1}:

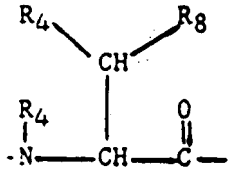


XL_{41}



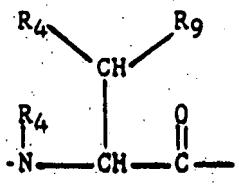
XL_{4a1}

wherein H_{131} is absent or a divalent moiety of the formula XL_{41}:



XL_{41}

wherein I_{14} is absent or a divalent moiety of the formula XL_5;



XL_5

wherein Z is $-N(R_{10})(OR_{14})$;

wherein R is

(a) isopropyl,

(b) isobutyl,

(c) phenylmethyl, or

(d) $-(CH_2)_p-C_3-C_7$cycloalkyl;

wherein R_1 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,

(c) C_1-C_5alkyl,

(d) C_3-C_7cycloalkyl,

(e) aryl,

(f) -Het,

(g) C_1-C_3alkoxy, or

(h) C_1-C_3alkylthio;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1-C_5alkyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) amino C_1-C_4alkyl-,

(e) guanidinyl C_1-C_3alkyl-,

(f) aryl,

(g) -Het,

(h) methylthio,

(i) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(j) amino;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) hydroxy,

(d) aryl,

(e) -Het,

(f) guanidinyl-C_1-C_3alkyl-, or

(g) -$(CH_2)_p$-C_3-C_7cycloalkyl;

wherein R_9 is

(a) hydrogen,

(b) hydroxy,

(c) amino C_1-C_4alkyl-, or

(d) guanidinyl-C_1-C_3alkyl-;

wherein R_{10} is

(a) hydrogen, or

(b) C_1-C_5alkyl;

wherein R_{11} is -R or -R_2;

wherein R_{13} is

(a) aryl,

(b) amino,

(c) mono-, di or tri-C_1-C_3alkylamino,

(d) -Het,

(e) C_1-C_5alkyl

(f) C_3-C_7cycloalkyl,

(g) C_2-C_5alkenyl,

(h) C_3-C_7cycloalkenyl,

(i) hydroxy,

(j) C_1-C_3alkoxy,

(k) C_1-C_3alkanoyloxy,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) -COOH,

(o) -CO-O-C_1-C_6alkyl,

(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(q) -CO-N$R_{22}R_{25}$;

(r) C_4-C_7cyclic amino,

(s) C_4-C_7cycloalkylamino,

(t) guanidyl,

(u) cyano,

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy-C_2-C_4alkyl)amino, or

(y) di-(hydroxy-C_2-C_4alkyl)amino;

wherein R_{14} is

(a) C_1-C_{10}alkyl,

(b) -$(CH_2)_n$-aryl,

(c) -$(CH_2)_n$-Het,

(d) -$(CH_2)_{n+2}$-R_{18},

(e) -$(CH_2)_{n+2}$-R_{19},

(f) (hydroxy-C_1-C_8alkyl), or

(g) (C_1-C_3alkoxy)C_1-C_8alkyl;

wherein R_{18} is

(a) amino,

(b) mono-, or di- C_1-C_3alkylamino,

(c) C_4-C_7cyclic amino; or

(d) C_4-C_7cycloalkylamino;

wherein R_{19} is

(a) aryl,

(b) -Het,

(c) tri-C_1-C_3alkylamino,

(d) C_3-C_7cycloalkyl,

(e) C_2-C_5alkenyl,

(f) C_3-C_7cycloalkenyl,

(g) hydroxy,

(h) C_1-C_3alkoxy,

(i) C_1-C_3alkanoyloxy,

(j) mercapto,

(k) C_1-C_3alkylthio,

(l) -COOH,

(m) -CO-O-C_1-C_6alkyl,

(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(o) -CO-$NR_{22}R_{25}$,

(p) guanidyl,

(q) cyano,

(r) N-cyanoguanidyl,

(s) cyanoamino,

(t) (hydroxy-C_2-C_4alkyl)amino,

(u) di-(hydroxy-C_2-C_4alkyl)amino; or

(v) -SO_3H;

wherein R_{20} is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_{21} is

(a) -NH_2, or

(b) -OH;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3alkyl;

wherein R_{23} is

(a) -$(CH_2)_n$-OH,

(b) $-(CH_2)_n-NH_2$,

(c) aryl, or

(d) C_1-C_3alkyl;

wherein R_{24} is $-(CH_2)_n-R_{13}$;

wherein R_{25} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein i is zero to two, inclusive;

wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein Q is

(a) $-CH_2-$,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-;

wherein M is

(a) -CO-, or

(b) $-CH_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{25}$,

(j) $CONHR_{25}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -N(R_4)-C_1-C_3alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl-C_1-C_4alkyl-,

(viii) amino, or

(ix) mono- or di-C_1-C_4alkylamino;

with the overall provisos that

(1) when R_{14} is C_1-C_3 alkyl, E_{10}-F_{11} does not include XL_6, XL_{6a}, XL_{6b}, XL_{6c}, XL_{6d}, XL_{6e} or XL_{6f};

(2) when R_{14} is C_1-C_3 alkyl, C_8-D_9 does not include XL_7, XL_{7a} or XL_{7b};

(3) when R_{10} is C_1-C_5 alkyl, one of G_{121}, H_{131} or I_{14} must be present;

(4) when X is R_5-CH_2-O-C(O)- and only D_9, E_{10} and F_{11} are present, R_5 is other than phenyl;

or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

7. A renin inhibitory peptide of claim 6

wherein X is

(a) R_5-O-CH_2-C(O)-,

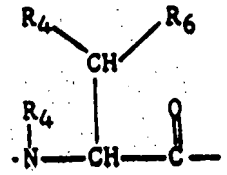
(b) R_5-CH_2-O-C(O)-,

(c) $R_5-(CH_2)_n-C(O)-$,

(d) $R_6-(CH_2)_1-C(O)-$, or

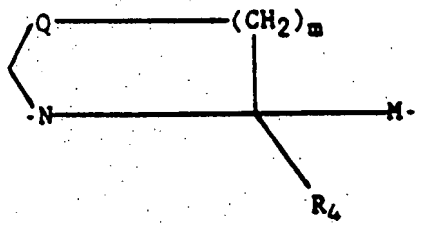
(e) $[R_6-(CH_2)_n]_2CH-C(O)-$;

wherein A_6 is absent or a divalent moiety of the formula XL_2



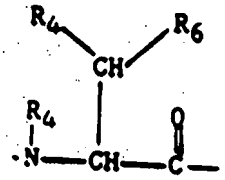
XL_2

wherein B_7 is absent or a divalent moiety of the formula XL_b



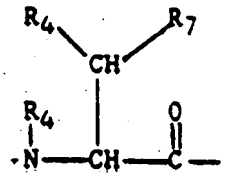
XL_b

wherein C_8 is absent or a divalent moiety of the formula XL_2



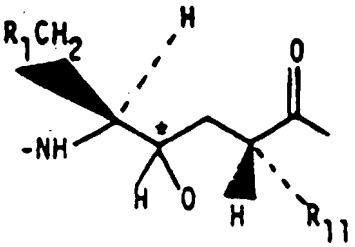
XL_2

wherein D_9 is a divalent moiety of the formula XL_3

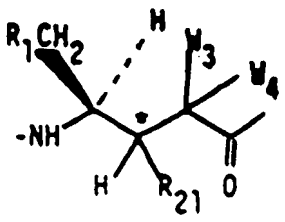


XL_3

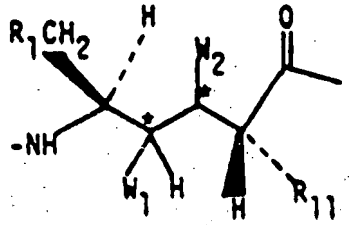
wherein E_{10}-F_{11} is a divalent moiety of the formula XL_6, XL_{6a}, XL_{6e}, XL_{6f} or XL_{6h}



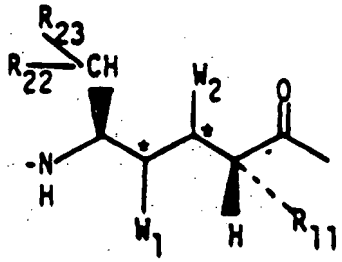
XL_6



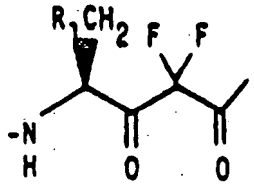
XL_{6a}



XL_{6e}



XL_{6f}



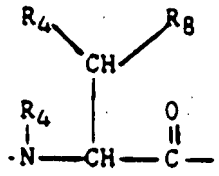
XL_{6h}

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein W_1 and W_2 are -OH or $-NH_2$;

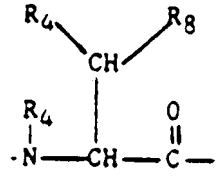
wherein W_3 and W_4 are -H or -F;

wherein G_{121} is absent or a divalent moiety of the formula XL_{41}



XL_{41}

wherein H_{131} is absent or a divalent moiety of the formula XL_{41}



XL_{41}

wherein I_{14} is absent;

wherein Z is $-N(R_{10})(OR_{14})$;

wherein R is

(a) isopropyl,

(b) isobutyl,

(c) phenylmethyl, or

(d) -$(CH_2)_p$-C_3-C_7 cycloalkyl;

wherein R_1 is

(a) C_1-C_5 alkyl,

(b) aryl, or

(c) C_3-C_7 cycloalkyl;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_5 is

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) aryl, or

(d) -Het;

wherein R_6 is

(a) -$(CH_2)_p$-aryl, or

(b) -$(CH_2)_p$-Het;

wherein R_7 is

(a) C_1-C_5 alkyl,

(b) amino C_1-C_4 alkyl-,

(c) guanidinyl C_1-C_3 alkyl-,

(d) aryl, or

(e) -Het;

wherein R_8 is

(a) C_1-C_5 alkyl,

(b) aryl, or

(c) -Het;

wherein R_{10} is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_{11} is -R;

wherein R_{14} is

(a) C_1-C_{10} alkyl,

(b) -$(CH_2)_n$-aryl,

(c) -$(CH_2)_n$-Het, or

(d) (hydroxy-C_1-C_8 alkyl);

wherein R_{21} is

(a) $-NH_2$, or

(b) -OH;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3 alkyl;

wherein R_{23} is

(a) aryl, or

(b) C_1-C_3 alkyl;

wherein i is zero to two, inclusive;

wherein m is one or two;

wherein for each occurrence n is independently an integer zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein Q is

(a) $-CH_2-$, or

(b) -CH(OH)-;

wherein M is -CO-;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{25}$,

(j) $CONHR_{25}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) $-N(R_4)$-C_1-C_3alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl-C_1-C_4alkyl-,

(viii) amino, or

(ix) mono- or di-C_1-C_4alkylamino;

with the overall provisos that

(1) when R_{14} is C_1-C_3 alkyl, E_{10}-F_{11} does not include XL_6, XL_{6a}, XL_{6e} or XL_{6f};

(2) when R_{10} is C_1-C_5 alkyl, G_{121} or H_{131} must be present;

(3) when X is R_5-CH_2-O-C(O)- and only D_9, E_{10} and F_{11} are present, R_5 is other than phenyl;

or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

8. A renin inhibitory peptide of claim 7

wherein X is

(a) R_5-O-CH_2-C(O)-,

(b) R_5-CH_2-O-C(O)-,

(c) R_5-$(CH_2)_n$-C(O)-,

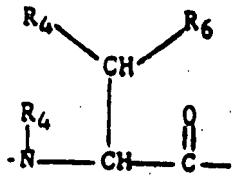
(d) R_6-$(CH_2)_t$-C(O)-, or

(e) $[R_6$-$(CH_2)_n]_2CH$-C(O)-;

wherein A_6 is absent;

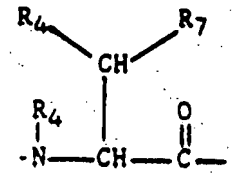
wherein B_7 is absent;

wherein C_8 is absent or a divalent moiety of the formula XL_2



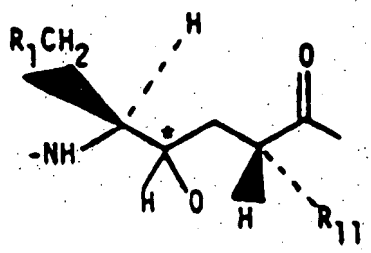
XL_2

wherein D_9 is a divalent moiety of the formula XL_3

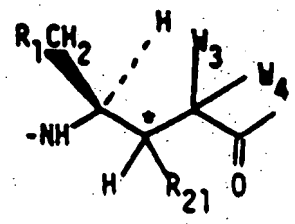


XL_3

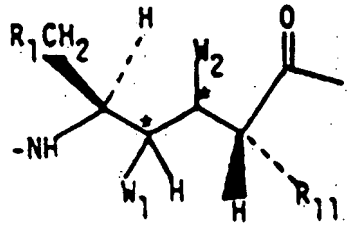
wherein E_{10}-F_{11} is a divalent moiety of the formula XL_6, XL_{6a}, XL_{6e}, XL_{6f} or XL_{6h}



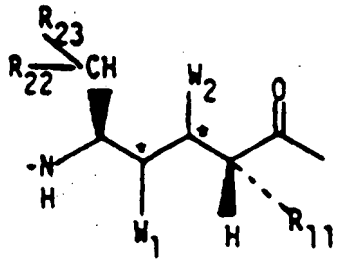
XL_6



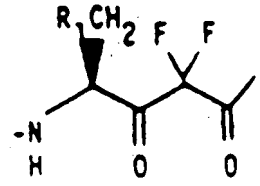
XL_{6a}



XL_{6e}



XL_{6f}



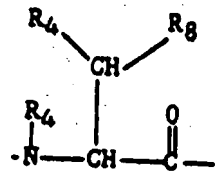
XL_{6h}

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein W_1 and W_2 are -OH or $-NH_2$;

wherein W_3 and W_4 are -H or -F;

wherein G_{121} is absent or a divalent moiety of the formula XL_{41}



XL_{41}

wherein H_{131} is absent;

wherein I_{14} is absent;

wherein Z is $-N(R_{10})(OR_{14})$;

wherein R is

(a) isopropyl,

(b) isobutyl,

(c) phenylmethyl, or

(d) $-(CH_2)_p$-C_3-C_7 cycloalkyl;

wherein R_1 is

(a) C_1-C_5 alkyl,

(b) aryl, or

(c) C_3-C_7 cycloalkyl;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_5 is

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) aryl, or

(d) -Het;

wherein R_6 is

(a) $-(CH_2)_p$-aryl, or

(b) $-(CH_2)_p$-Het;

wherein R_7 is

(a) C_1-C_5 alkyl,

(b) amino C_1-C_4 alkyl-,

(c) guanidinyl C_1-C_3 alkyl-,

(d) aryl, or

(e) -Het;

wherein R_8 is

(a) C_1-C_5 alkyl,

(b) aryl, or

(c) -Het;

wherein R_{10} is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_{11} is -R;

wherein R_{14} is

(a) C_1-C_{10} alkyl,

(b) -$(CH_2)_n$-aryl,

(c) -$(CH_2)_n$-Het, or

(d) (hydroxy-C_1-C_8 alkyl);

wherein R_{21} is

(a) $-NH_2$, or

(b) -OH;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3 alkyl;

wherein R_{23} is

(a) aryl, or

(b) C_1-C_3 alkyl;

wherein i is zero to two, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{25}$,

(j) $CONHR_{25}$,

(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl-C_1-C_4alkyl-,
(viii) amino, or
(ix) mono- or di-C_1-C_4alkylamino;

with the overall provisos that

(1) when R_{14} is C_1-C_3 alkyl, E_{10}-F_{11} does not include XL_6, XL_{6a}, XL_{6e} or XL_{6f};

(2) when R_{10} is C_1-C_5 alkyl, G_{121} must be present;

(3) when X is R_5-CH_2-O-C(O)- and only D_9, E_{10} and F_{11} are present, R_5 is other than phenyl;

or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

9. Boc-Phe-His-Sta-Ile-NHOCH$_2$-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[2-methyl-1-[[(phenylmethoxy)amino]carbonyl]butyl]amino]-1-(2-methylpropyl)-4-

oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R)]]-, a compound of claim 8.

10. Boc-Phe-His-Sta-Ile-NHOCH$_3$, or L-Histidinamide, N-[(1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[-[(methoxyamino)carbonyl]-2-methylbutyl]amino]-1-(2-methylpropyl)-(4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

11. Boc-Phe-His-Sta-Ile-NHOC$_2$H$_5$, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-[[1-[(ethoxyamino)carbonyl]-2-methylbutyl]amino]-2-hydroxy-1-(2-methylpropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

12. Boc-Phe-His-Sta-Ile-NHO-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[2-methyl-1-phenoxyamino)carbonyl]butyl]amino]-1-(2-methylpropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

13. Boc-Phe-His-Sta-Ile-NHO-(p-nitrobenzyl), or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[2-methyl-1-[[[(4-nitrophenyl)methoxy]amino]carbonyl]butyl]amino]-1-(2-methoxypropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R)]]-, a compound of claim 8.

14. Boc-Phe-His-LVA-Ile-NHOCH$_2$-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(phenylmethoxy)amino]carbonyl]butyl]amino]carbonyl]-1-(2-methylpropyl)hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-, a compound of claim 8.